Impact of US & EU Pediatric Legislation

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Impact of US & EU Pediatric Legislation

- US FDAAA & predecessors
- EU Pediatric Regulation
- ICH E 11
- ICDRA
- Other countries & regions
Impact of US & EU Pediatric Legislation

- Few industry boards without ped debate
- Presentations start less with Adam & Eve
- A&E presentations usually repetitive
- Emphasis on ‘nuts & bolts‘ of PIPs/PPs
- Background knowledge remains essential
- Now 14 years FDAA experience and 3½ years experience with EMA / PDCO
- Two key expertises needed: (1) content of pediatric drug development; (2) pediatric procedural experience FDA / EMA PDCO
Impact On What?

- Child health & parents‘ health
- Big pharma: Costs per department/ company/ industry
- EMA
- Academia
- Pediatric Learned Societies
- Reimbursement institutions
- Pediatric Research Networks
- Consultancy companies
- CROs
- Emerging new business
Child Health & Health Of Their Parents

• FDA 2001 Status Report to Congress*: “Superior drug treatment information is expected to permit quicker recoveries from childhood illnesses, with fewer attendant hospital stays, physician visits and parental work days lost.“

• No such statistics so far
• FDA& EMA statistics on new trials, label changes etc.
• Points missing: QoL endpoints, child survival
→Not all improvements are measurable

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

Basic Research → Entry into Man → Proof of Concept (PoC) → Phase II+III → Registration 1st Country → Patent-protected Market → EU Pediatric Investigation Plan (PIP): mandatory at end of human PK → Patent Expiry → Generic Competition

FDA: Early dialogue recommended; Ped Plan mandatory at submission
Capturing PIP Costs Across A Company

• Flexible time usually booked ‘somewhere’
• Few companies have dedicated pediatric FTE
• Learnings from pediatric theme # across projects:
  - Usually, themes are abandoned if below threshold
  - Even if maintained, of limited value
  → High costs where large programs reach execution
  → Underreporting of early PIP brainstorming & preparing
  → Discrepancy: workload seen by individuals vs. numbers
  → In comparison to overall costs PDD planning costs low
  → Even semi-precise cost estimate will take years
PIP Costs: Regulatory Consulting

- Regulatory PIP preparation: 200-300 hours
- Reg consulting only; clinical input by requesting company
- Deeper clinical input needed: easily be 3 – 5 times these hours
- Fees depend of seniority of consultant involved
- Does still not include efforts of sponsoring company and specifically not PIP execution, i.e. performing of studies etc.
PIP Costs: Execution

• With 20 – 30 thou € / patient real costs, a study with 100 adult subjects costs 2 – 3 Mio €

• Multiply that with factor P in trials in children

• Higher number of subjects correspond to higher costs

• Potential additional costs: Juvenile Animal studies, developing a pediatric formulation, establish of a registry, etc.

• Rule of the thumb for BD&L, e.g. for a product without pediatrics done so far: 20 Mio € (Including trial execution)

• This money needs to be invested today / after adult registration. Reward will come much later
Initial Barriers In Pharmaceutical Industry

• Lack of preparedness & disbelief
• Handling of different child diseases by adult teams, e.g. oncology: demanding, complex,
• Rare & ultra-rare pediatric target disease outside adult use for ½y PE or SPC prolongation: challenging
• Initial disregard of functions, e.g. preclin tox & s; tech dev; resulted in suboptimal handling → higher EMA demands
• Territorial fighting: who coordinates pediatrics? – Could be regulatory, clinical, project management, marketing, others
The Landscape Today (1)

- Disbelief has disappeared in big pharma
- Small EU, non-EU-companies continue learning, e.g. regulatory lone warrior brings the bad news to the CEO‘s attention
- Technical Development: EUPFI
  www.pharmacy.ac.uk/fileadmin/documents/Practice_and_Policy/EuPFI_European_Paediatric_Formulation_Initiative.pdf
- Preclin Tox&Safe/ Juv Animals: ILSI HESI 5/6th May Wash DC
  http://www.hesiglobal.org/i4a/pages/index.cfm?pageid=3496
- Rare & ultra-rare pediatric diseases: Parties still struggling
- Help often asked for after 1st PIP submission by company alone
The Landscape Today (2)

- WHO has started ped initiative – Make Medicines Child Size
- All reg agencies have focus on use of drugs in children -ICDRA
- FDA & EMA monthly TCs, exchange of personnel
- Other regions, including Japan, Canada, Australia observe & start cooperation with EMA & FDA
- Review of ICH E 11 will come eventually
Continuously New Procedures, Forms, & More

- For new indications not covered by class waivers, company can submit new PIP or modify old PIP. Modification is faster; new PIP does not jeopardize ongoing PIP negotiation.
- Continuous evolution of forms & procedures.
- E.g. PIP submission now possible completely electronically.
- E.g. clinical trial outlines, standard PIPs.
- FDA pediatric website with new design.

→ Need to check both ped websites regularly for news.
Pediatric Drug Development As Career Option

- EMA pediatric team now with ~ 25 officers considerable size
- Industry scientists are also hired by FDA
- FDA officers, EMA coordinators & PDCO members are exposed to fascinating array of endeavours of drug development
- Industry employees only see their respective projects
- Industry organisations, e.g. EFPIA, see more, but anonymized
- Consultants see more projects at early stages
- CROs will seem them when they reach execution stage
- EMA employees do stages @ FDA & vice versa

→ Opportunities in clinic, science, industry, regulatory, & more
- No adequate coverage yet by lay press & media
EU Legislation Can Block Registration: Decision 1st Instance of EU Court of Justice (EuCJ)

- Company submitted ultrasound contrast medium for coronary artery disease (CAD)
- PDCO: heart malperfusion exists in children → reflect about potential pediatric use
- Company refused → negative PDCO opinion → no MAA validation → sued @ 1st instance EuCJ
- 1st instance EuCJ rejected request to suspend EMEA decision to deny waiver & interim measures. Main case still pending
Business Development & Licensing (BD&L)

• Big pharma‘s productivity is not sufficient
• Start-ups replenish the pipe line
• Need to consider pediatrics in BD&L
• EU: BD&L package without PIP 20 Mio € worth less
• A company that licenses in and receives negative EMA opinion(s) damages its attractivity
→ EMA/PDCO role includes performing quality checks for BD&L capabilities
**PIP Withdrawal**

- As long as no PDCO decision you can withdraw PIP
- With a PDCO opinion it’s out the company’s hands: you must comply or modify the PIP
- Project abandoned after PDCO opinion: justify & inform
- Otherwise, you might be held in contempt of EMA/PDCO
Academic Pediatric Research Networks

- Many EU pediatric research networks exist & expand
- EMEA coordinates meta-network; FP7 will support
- Industry: more experience w disease-specific networks
- Role of national networks still open – will we need 27?
- Pediatric societies: discrepancy between enthusiasm from @ top & relatively low interest of practitioners
- Still limited interest for pediatric clinical trials
- A multitude of subliminal changes is evolving
- Many more changes will take a lot of more time
Companies & Pediatrics

• With growing market & funding, medicines for children will attract inventive personalities

• EU examples: Therakind, O4CP

• Many PIPs are reaching execution phase

• Most trials are executed by CROs

• European CRO Federation EUCROF pediatric working group
Reimbursement Institutions & Prices

- So far children’s pharmaceutical treatment is strongly based on generics
- Commercials in pediatric journals focus on generics
- Reimbursement institutions have so far scarcely joined the discussion
- PUMA medications will be much more expensive
- Reimbursement institutions will have to adapt
Regulatory Consultancies

• High need for regulatory & clinical consulting
• Most clients SMEs EU; all sizes from outside of EU
• Increasingly, companies approach us after PIP on their own; PIP handling is difficult without expertise in (1) pediatric drug development & (2) procedural experience with EMA, PDCO, FDA & others
• Quality will drive selection of the fittest
EU vs. US / EMA vs. FDA

- US started when many blockbusters were at peak sales. Now pediatric consideration required early
- FDA often perceived as more pragmatic, but depends
- Considerable convergence FDA ↔ EMA
- Is additional burden to drug development. Not unbearable in view of to the entire drug dev process
- Can be very tough for individual companies
- Might keep some innovative drugs from the EU market
- At present, EU is more a problem for US companies than vice versa; US companies will learn
Burden For Industry: SMEs, Big Pharma

• Before EU regulation open dialogue – enthusiastic young industry employees, clinicians, regulators
• EU industry failed to pediatrics for re-positioning itself
• Not individual failure. Reflects limitation of an adjunct to adult development in a commercial environment
• With additional billions in science research we could develop more drugs for rare diseases – what’s new?
• Pediatric legislation strives to improve something in an imperfect world. Occasional exaggerations happen.
• Shows also non-uniformness of EU states
Pediatrics & EU

- EU is not a uniform cultural landscape
- Large language areas switch less easily to English
- The level of science in EU states differs considerably
- Innovative vs. conservative forces are everywhere
- European institutions are very resistant to change
- EU citizens complain – and for whom do they vote?
- Not all scientifically & technically doable is done
- We see this through the ‘pediatric glasses‘. Europe will change, eventually …. still at our lifetime?
Conclusions

• US legislation was 1st step. EU goes further, wants ped indication → consider use in children early
• PIP can be bottleneck or roadblock for new drugs → should be handled by knowledgeable person / team
• Those who do not want to learn are punished
• Pediatric drug development is becoming an essential part of the general drug development process
• Not all outcomes are easy to measure
• Working relation between industry & EMA/PDCO not yet partnership as would be possible & desirable
• Continuing dialogue between the partners essential
The EFGCP Children’s Medicines Working Party and DIA Europe are pleased to announce their second joint paediatric conference. Traditional paediatric meetings of both societies in the past and the joint meeting in 2009 have attracted top level speakers from the European Medicines Agency (EMA), FDA, national authorities, WHO, academia, pharmaceutical industry and parents & patients’ organizations. This second joint program will again offer the opportunity for intensive discussion among stakeholders in different topics relevant for pediatric medicines. We will address visions, daily challenges and ways forward in paediatric drug development. On this basis, the conference will also offer excellent networking opportunities for all attendees.

The conference will include three parallel breakout sessions on each day for a lively interactive discussion. Furthermore, it will provide participants with the opportunity of asking questions by e-mail before the conference and during the morning of day 1, which will be in the afternoon addressed by a speaker panel chaired by Paolo Tomasi, European Medicines Agency (EMA).
Thank You For Your Attention!
Back-Ups
Guide to Paediatric Drug Development and Clinical Research

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