

Current regulatory developments on products in paediatrics

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Op de kleintjes letteren

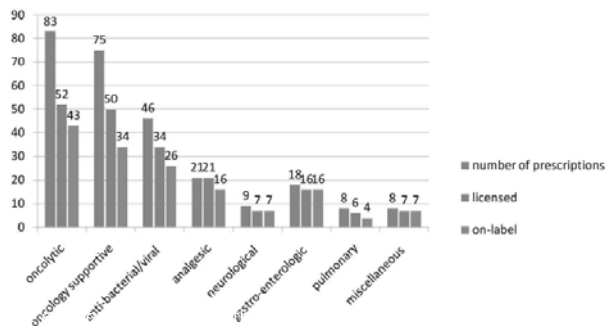
Henk van den Berg

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Op de kleintjes letteren

Rationale for the Legislation

- 50-90% of the medicinal products currently used in paediatrics (up to age 18) have not been studied or authorised for such use
- 20% of the EU population, i.e. 100 million, is aged less than 16 years



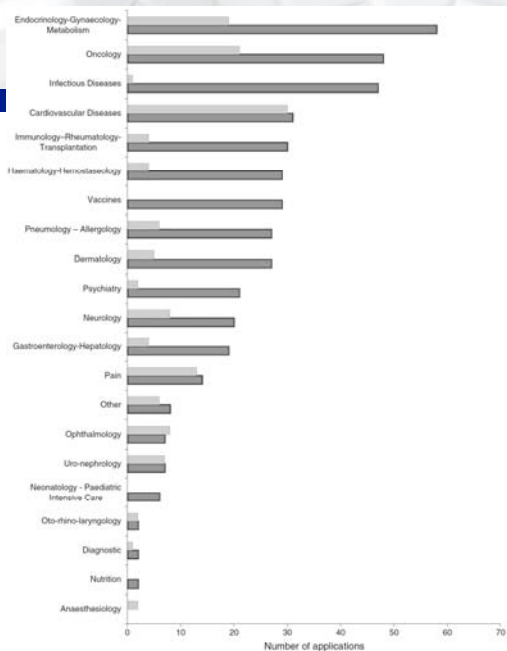
Objectives of the Regulation

- Improve the health of children
 - *Increase high quality, ethical research for medicines in children*
 - *Increase the availability of authorised medicines for children*
 - *Increase information on medicines for children*
- The above should be achieved without
 - *unnecessary studies in children*
 - *delaying the authorisation for use in adults*

Benefits for oncology at least

- *Study in younger age ranges (PK and safety data)*
- *Age-appropriate formulations*
- *Long-term follow-up data*
- *Earlier consideration of medicines for paediatric use*

Number of applications:
gray full waivers



Investigation plans covering these age groups	Proposed	Accepted by PDCO	Requested by PDCO	Covering these age groups after requests by PDCO
12–18 years	76% (41/54)	37	7 ^a	81% (44/54)
6–11 years	67% (36/54)	33	7	74% (40/54)
2–5 years	46% (25/54)	24	5	54% (29/54)
Partial coverage	9% (5/54)	4	3	13% (7/54)
28 days–23 months	28% (15/54)	12	7 ^b	35% (19/54)
Partial coverage	17% (9/54)	6	3	17% (9/54)
0–27 days	15% (8/54)	7	7	26% (14/54)
Following a staggered approach	11% (6/54)	6	5	20% (11/54)

Phase II/III studies

Clinical trial design parameters	Proposed	Accepted by PDCO	Requested by PDCO	Total
Number of trials	62 (100%)	61	23 (100%)	85 (100%)
Randomised trials	50 (81%)	50	18 (78%)	68 (80%)
Double-blind	33 (53%)	32	11 (47.8%)	44 (52%)
Placebo controlled	12 (19%)	12	12 (52.2%)	24 (28%)
Active controlled	35 (57%)	35	6 (26.1%)	41 (48%) ^a
Active+placebo	4 (7%)	4	0	4 (5%)

PIPs published for Oncology

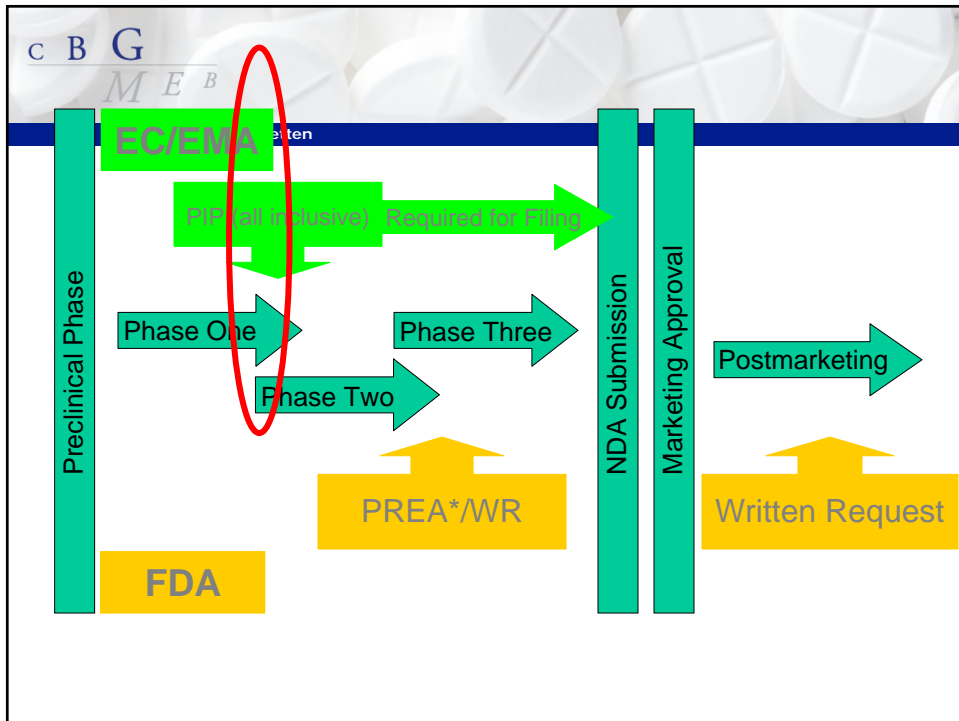
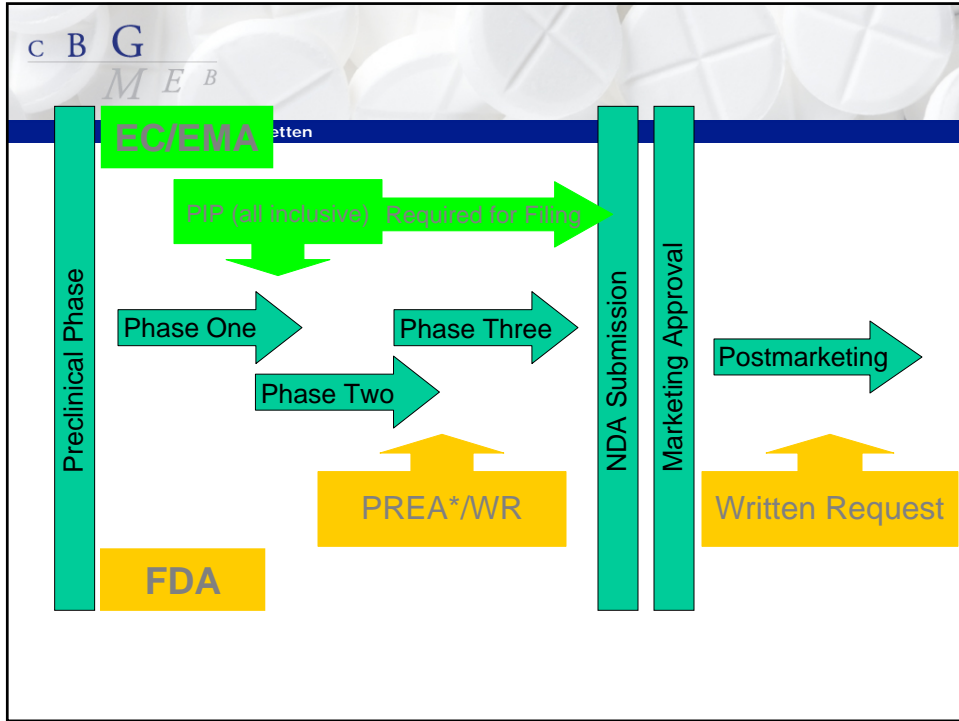
- Overall: 52
- With waiver: 19



In 2010/2011: 12/9 = Oncology

Studies requested in 9 PIPs

- Quality: 5 (e.g.: age appropriate formulation)
- Non-clinical: 16 (e.g.: juvenile development toxicity study, repeat-dose toxicity study, toxikokinetic, in vitro studies)
- Clinical: 26 (e.g.: pharmacokinetic study, dose-finding study, tolerability study, randomized controlled /blinded/un-blinded, placebo/active control)



Differences between Europe and USA Paediatric Processes

- **Europe:** filing can be denied if it does not have a paediatric plan, waiver or deferral; not possible in US
- **Europe:** process is asking for more definitive information **early** in development process
- **USA:** has 2 separate processes (incentive and requirement) that are only partially unified while Europe's paediatric process is unified under the new legislation
- **USA:** Mandated **paediatric focused review** of post marketing adverse events
- **USA:** Can **ask for more indications**

Academia interaction

• EMA and Pharma

- **A drug-driven process**
- For a given drug,
- identify the needs
- Identify the disease, mainly impacted by the issue of similarities with adults
- a PIP or Waiver/a drug approved for a paediatric indication

• Paediatric Academia

- **A disease driven process**
- For a given disease,
- Identify and prioritize relevant targets and pathways
- Find the most relevant drugs
- A therapeutic strategy that integrate new drugs



- **Main risks due to only partially overlapping interests**
 - **Versus industry**
 - **Products are not developed due to increased costs**
 - **Products not registered (= assessed) for specific indications**
 - **Patient risks due to off label use**
 - **Patients not treated due to non-reimbursement**
 - **Versus academia / learned societies**
 - **Patients not available for studies**
 - **Interference with programmes**

Problems

- Early submission resulting in discussion after phase 1 of
 - Formulation (route of administration, dosage, excipients, preservatives, colouring, etc)
 - Toxicology (age ranges, juvenile toxicity testing, etc.)
 - Full paediatric programme (type of studies, statistics without knowing the effect size, duration of the studies, follow-up)
 - No data on extrapolation from adults
 - The PIP has to be modified several times (only on request of the company !!)



March 2011

- > 1000 PIPs considered
- 434 agreed
- 370 still under discussion
 - Remainder withdrawn
- 200 modifications to agreed PIPs

Solutions?

Solution 1 Towards Academia / Learned societies Model PIP

- (To be) Discussed with learned societies
- Uniformity in for the several products for the same condition / indication

Preclinical studies

- in vitro and xenograft studies
- short and long term toxicity studies
- juvenile animals studies
- reproductivity test
- For non-cytostatic drugs
 - carcinogenicity test
 - mutagenic test
 - immunogenicity.

Clinical studies

Indications

- De novo AML
- Relapsed AML
- Acute promyelocytic AML
- AML in Down syndrome
- Secondary AML

Age ranges

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Type of studies

The type of clinical studies varies according to indication due to incidence and possibilities to extrapolate from adults.

Indication	Phase 1 / 2 studies	Phase 3 studies	Safety studies
De novo AML	x	x	x
Relapse AML	x	x	x
APL	x	x	x
Down syndrome related AML	x	x	x
Secondary AML	x	-	x

Number of patients

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Timing of the studies:

Studies can be scheduled as soon as dosing can be extrapolated from adults. An acceptable sequential approach is to start studied in relapsed and resistant patients first, followed by high risk newly diagnosed patients followed by standard risk newly diagnosed patients.

Solution 2 ?? Based on legislation EC guideline (2008/C 243/01)

➤ Condition

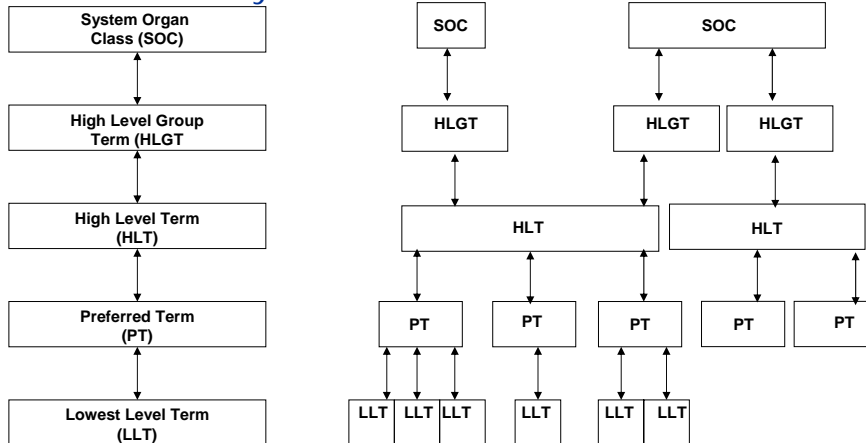
“Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome)”

➤ PIP indication

“The proposed indication(s) in the paediatric population for the purpose of a paediatric investigation plan,

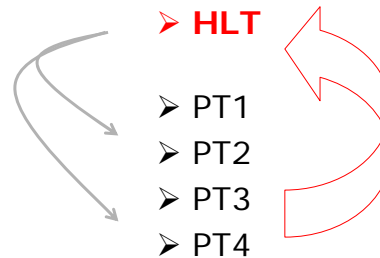
- ICD-10 (International Classification of Diseases)
- MESH (Medical Subject Headings, National Library US)
- MeDRA (Medical Dictionary for Regulatory Activities)

MedDRA Hierarchy



Principal Steps

1. Analysis of proposed condition/indication
2. Determination of corresponding HLT as 'ceiling'
3. Discussion of indications included under HLT
4. **Determination of indication(s) to be studied in the PIP**
5. PIP-opinion = HLT, automatically covering all PTs below HLT



Example anaesthesia-fospropofol

	Code	Term	Level
	10002092	Anaesthesia and allied procedures	HLT
	10067564	Anaesthesia procedure	PT
	10057616	Anaesthesia reversal	PT
	10058073	Anaesthetic premedication	PT
	10015011	Epidural anaesthesia	PT
	10067174	Epidural test dose	PT
	10052018	Facet joint block	PT
	10018060	General anaesthesia	PT
	10059251	Hypotensive anaesthesia procedure	PT
	10021723	Induction and maintenance of anaesthesia	PT
	10021724	Induction of anaesthesia	PT
	10021945	Infiltration anaesthesia	PT
	10024458	Light anaesthesia	PT
	10024758	Local anaesthesia	PT
	10025445	Maintenance of anaesthesia	PT
	10057286	Neuromuscular blockade reversal	PT
	10050293	Reversal of sedation	PT
	10059283	Sedative therapy	PT
	10049124	Sedation during medical procedure	LLT
	10039899	Sedation intra op	LLT
	10059283	Sedative therapy	LLT
	10041536	Spinal anaesthesia	PT

- Condition proposed by applicant: "Sedation"
- PIP indications proposed:
 - Procedural sedation 3-18 yrs
 - Maintenance of general anaesthesia 0-3 yrs
 - PDCO: both in all age groups
 - medDRA

Solution 3 Staggered approach

