The EU paediatric medicine regulation: is it working?

candid

A view from a paediatric oncology network

Bruce Morland

Birmingham Children's Hospital &

Innovative Therapies for Children with Cancer

Stress Reduction Kit

Directions:
1. Place kit on FIRM surface.
2. Follow directions in circle of kit.
3. Repeat step 2 as necessary, or until unconscious.
4. If unconscious, cease stress reduction activity.

The EU Pediatric Medicine Regulation:

- A EU political decision in December 2000
  to improve health of children in Europe
  Principle : obligation/incentives/rewards
- A Regulation launched in January 2007
  Paediatric Investigation Plan (PIP)
  Waiver
  Deferral
- A Paediatric Committee working at EMA since July 2007

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Drug	Disease	MA	itcc
adenoTK	High Grade Gliomas	N	
L-asparaginase	ALL	N	
Docetaxel	NPC	Y	
Bevacizumab	RMS	Y	X
Aprepitant	vomiting	Y	
Ipilimumab	solid tumors	N	
Vandetanib	Thyroid	N	
Everolimus	Sub Ep Astro	Y	
Casopitant	vomiting	Y	
Plerixafor	HSC mobilisation	Y	X
Sunitinib	GIST	Y	X
Nilotinib	CML	Y	X
6-mercaptopurine	ALL	Y	
IGF1R MoAb	Ewing tumors	N	X
Rituximab	NHL	Y	X
Linifamib	solid tumors	N	
Fosaprepitant	vomiting	Y	
Denosumab	bone metastatsis	Y	
Dasatinib	CML, Ph+ALL	Y	X
Bosutinib	CML	N	
L-asparaginase	ALL	N	
Deforolimus	solid tumours	N	
Cediranib	HGG	N	
Decitabine	AML	N	

24 drugs with an approved PIP in oncology

(as of 12/2010)

(13 already marketed in adults)

5 cytotoxic agents

3 anti-emetic agents

13 targeted agents

2 other compounds

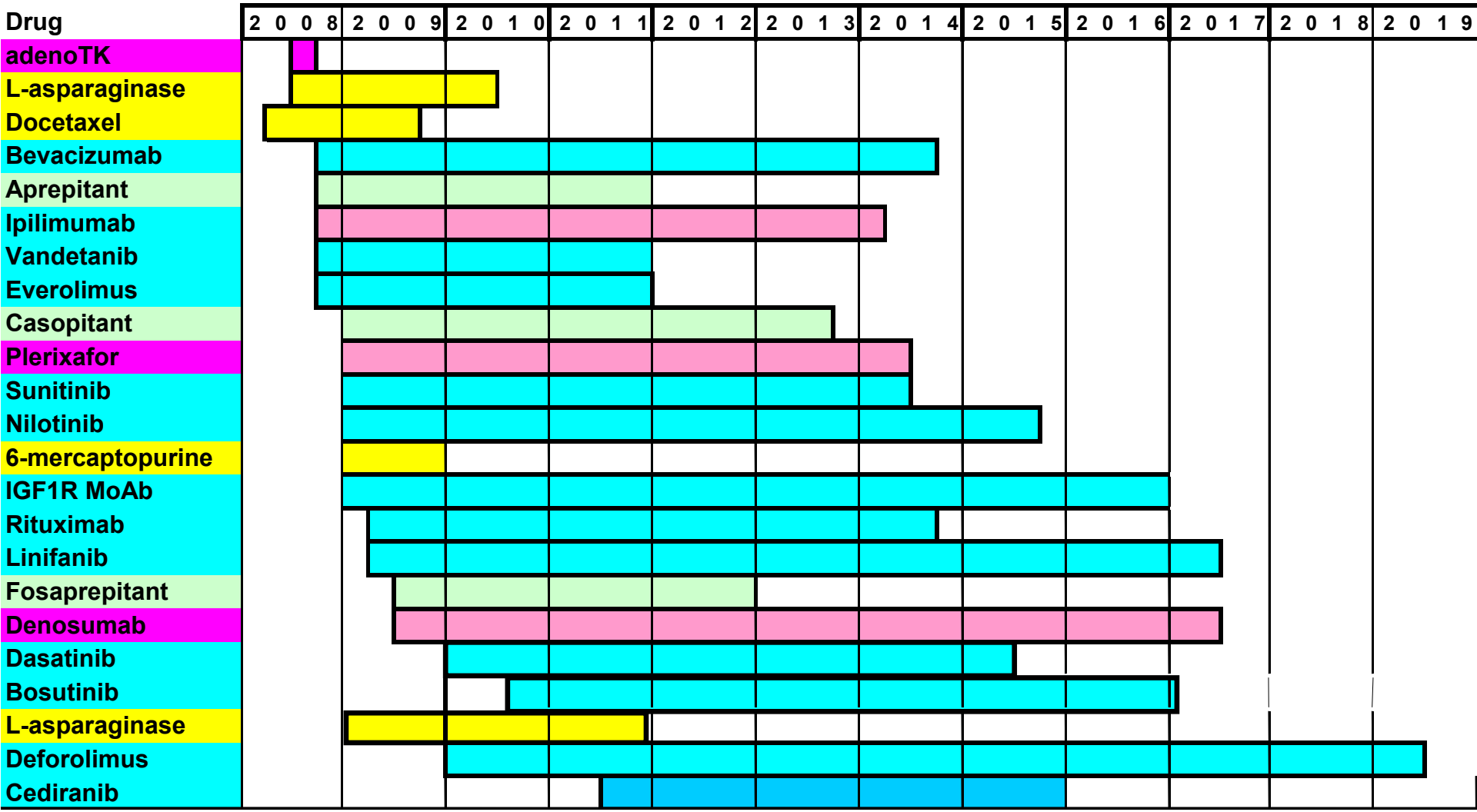
1 gene therapy product

NOT all PIPs will be completed

19 Waivers

Data from EMA website

PIPs of oncology drugs (as of 12/2010)



NOT all PIPs are ongoing

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- 6 drugs (25%) in very/extremely rare pediatric malignancies:
  - ✓Nasopharyngeal carcinoma
  - ✓Thyroid cancer
  - ✓GIST
  - ✓CML
  - ✓Sub Ep Astro
  - ✓ALL Ph+

- 3 drugs in solid tumors

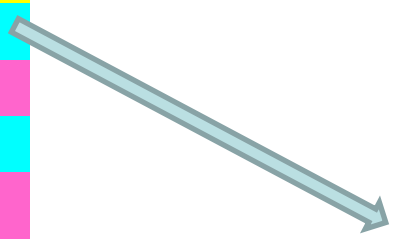
- Only one drug in « true » paediatric malignancy

- No drug in neuroblastoma, medulloblastoma, BSG etc

Data from EMA website 12/2010

Waivers

Drug	Disease
Novartis compound	Myelofibrosis/PCV
Geldanamycin	GIST
Arzoxifene	Osteoporosis
Bortezomib	Mantle cell lymphoma
Mesothelium chimeric Ab	Mesothelioma
Anti-Il6 Ab	Castleman's
Cinacalcet	Parathyroid Ca
Everolimus	Renal/pancreatic/carcinoid
Forodesine	CTCL
Ingenol	SCC
Lapatinib	H+N
Lenalidomide	MDS
Omacetaxine	Ph+ALL
Panobinostat	CTCL
Patupilone	Genital/peritoneal
Pemetrexed	H+N
Ralitrexed	Mesothelioma
Sorafenib	Thyroid



- HSP90 inhibitor
- Generic target

GIST story

- Geldanamycin - « no significant benefit over existing treatment »
- Nilotinib – « clinical studies not feasible/rarity »
- Sunitinib – PIP

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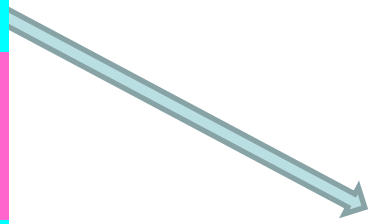

- Proteosome inhibitor
- Generic target
- Phase I in children in USA
- Phase II in HD in children in USA

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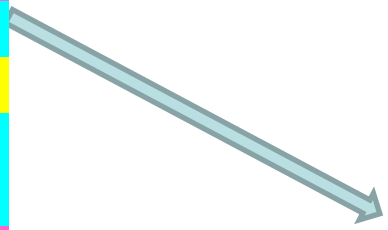

- mTOR inhibitor
- Generic target
- PIP in tuberose sclerosis/GCA

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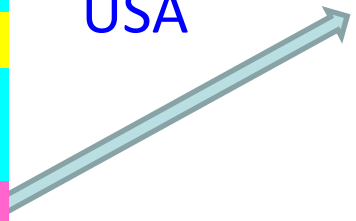
- « likely to be unsafe »
- Phase I study in children with solid tumours and MDS in the USA



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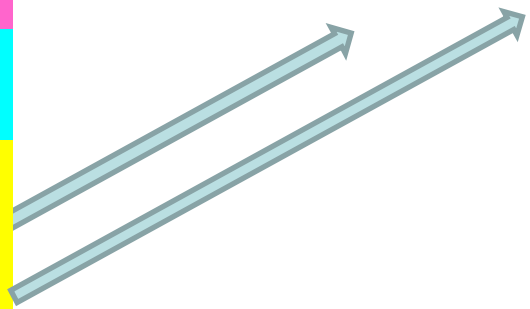
- Antifolate (methotrexate)
- Generic antimetabolite
- Phase I&II study of pemetrexed in solid tumours in USA



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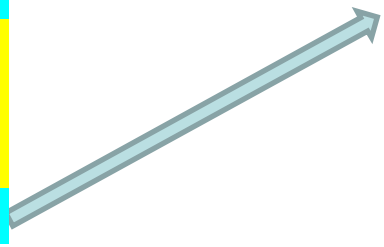
- Raf/VEGF/PDGFR
- Generic targets
- Phase I&II studies in solid tumours and ALL in USA
- In regular use in young patients with hepatocellular Ca



The EU regulation and Paediatric Oncology : the positive impact

- A dynamic but weighty process, with a significant workload for everyone involved

  41 oncology drugs with an opinion (24 PIPs, 19 waivers) and XX drugs without an opinion

- A field of specific interest for EMEA and PDCO

  Paediatric Oncology Task force (EMA, PDCO Members, Experts from academia) co-chaired by R. Herold and G. Vassal

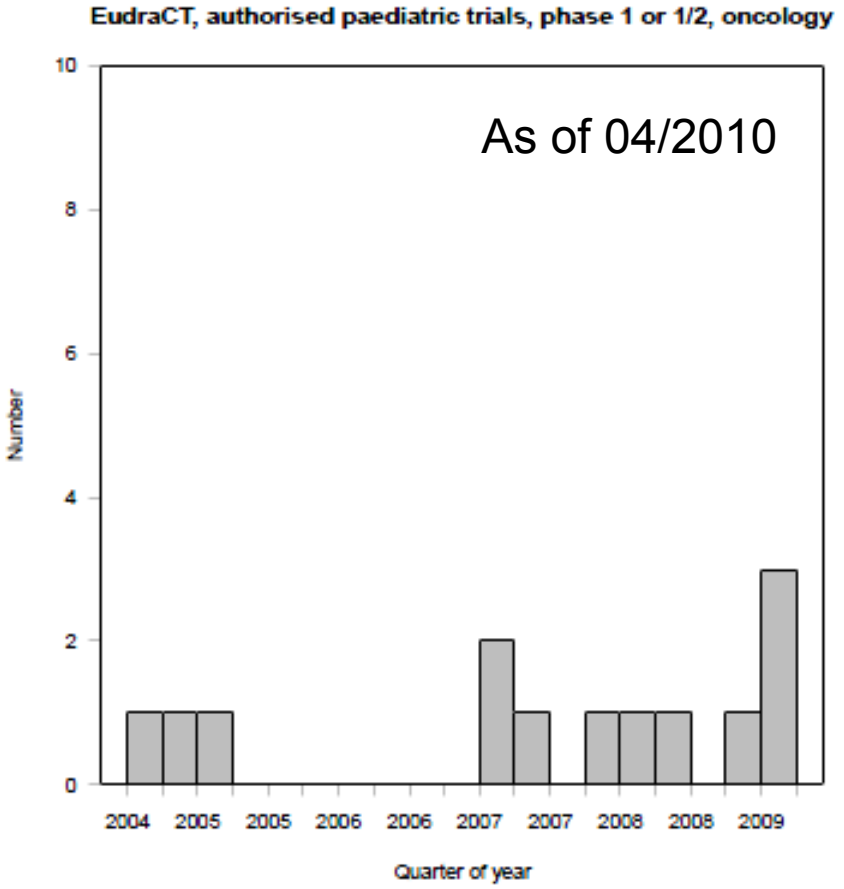
- Paediatric oncology is now a topic addressed by most Pharmaceutical Companies

  in your company, is there anyone with a job title including the word 'Paediatric'?

- A significant increase in contacts between Paediatric Oncology community and Pharma in Europe

The EU regulation and Paediatric Oncology: the issues in 2010 (1)

- No increase in the number of oncology drugs in early phase studies, still a major difference with the US
- The most clinically relevant diseases are not yet adequately covered



Courtesy of Ralf Herold

The EU regulation and Paediatric Oncology: the issues in 2010 (2)

- For Companies, paediatric development = a regulatory issue to comply with rather than a strategic R&D programme in its own right.
- Most PIPs take insufficiently account of current therapeutic strategies developed by cooperative groups
- The feasiblity of some PIPs is jeopardized by rarity of patients or drugs in competition.
- Each of the 60 pediatric malignancies is a very complex entity: Access to the most recent expertise is crucial to design the most appropriate investigation plans.

The challenge :Two processes that need to be harmonized and integrated

EMA and Pharma

- A drug-driven process

For a given drug,

- Identify the need
- Identify the disease, primarily driven by the similarities with adult cancer
- a PIP or Waiver/a drug approved in a paediatric indication

Ped Onc Academia

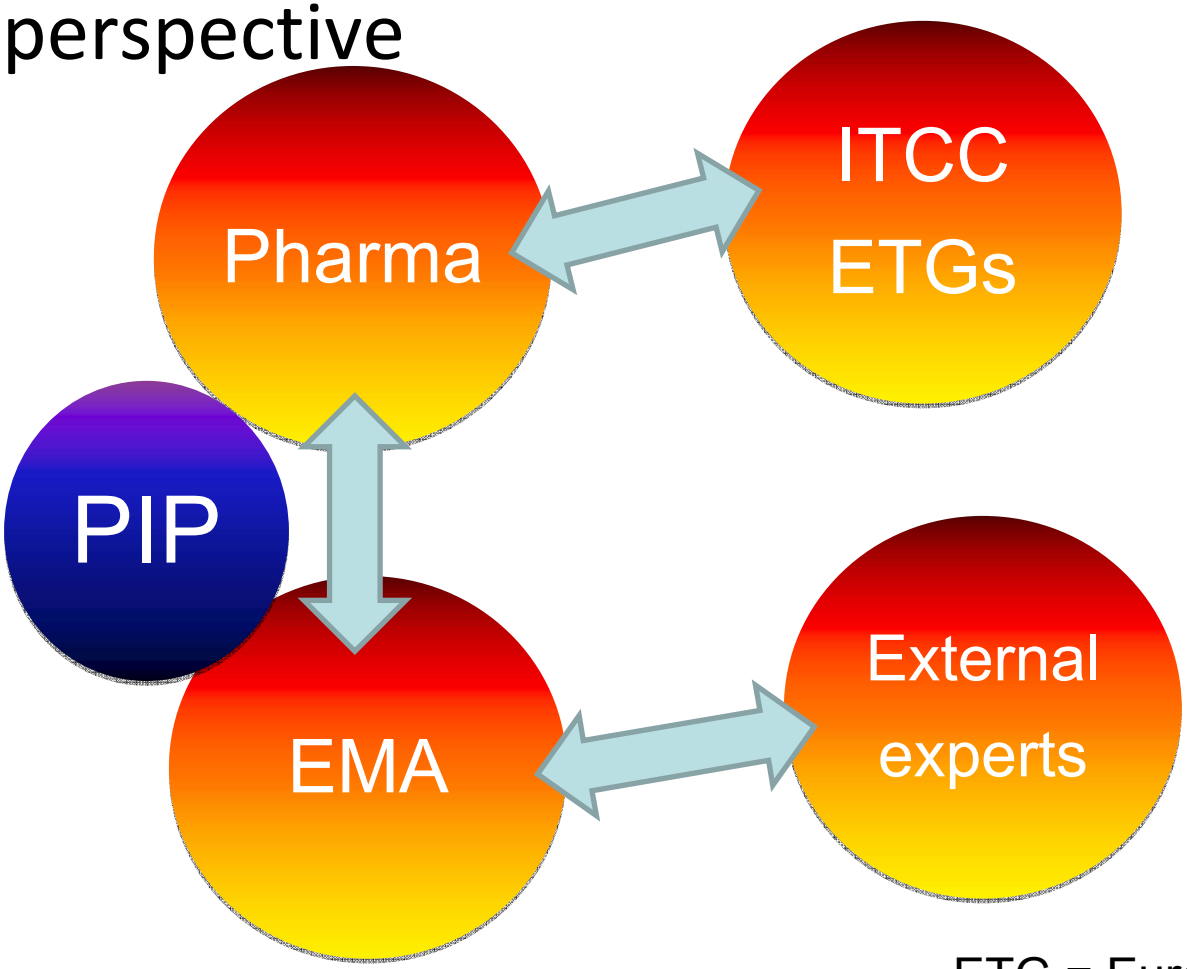
- A disease driven process

For a given disease,

- Identify and prioritize relevant targets and pathways
- Find the most relevant drugs
- A therapeutic strategy that integrates new drugs

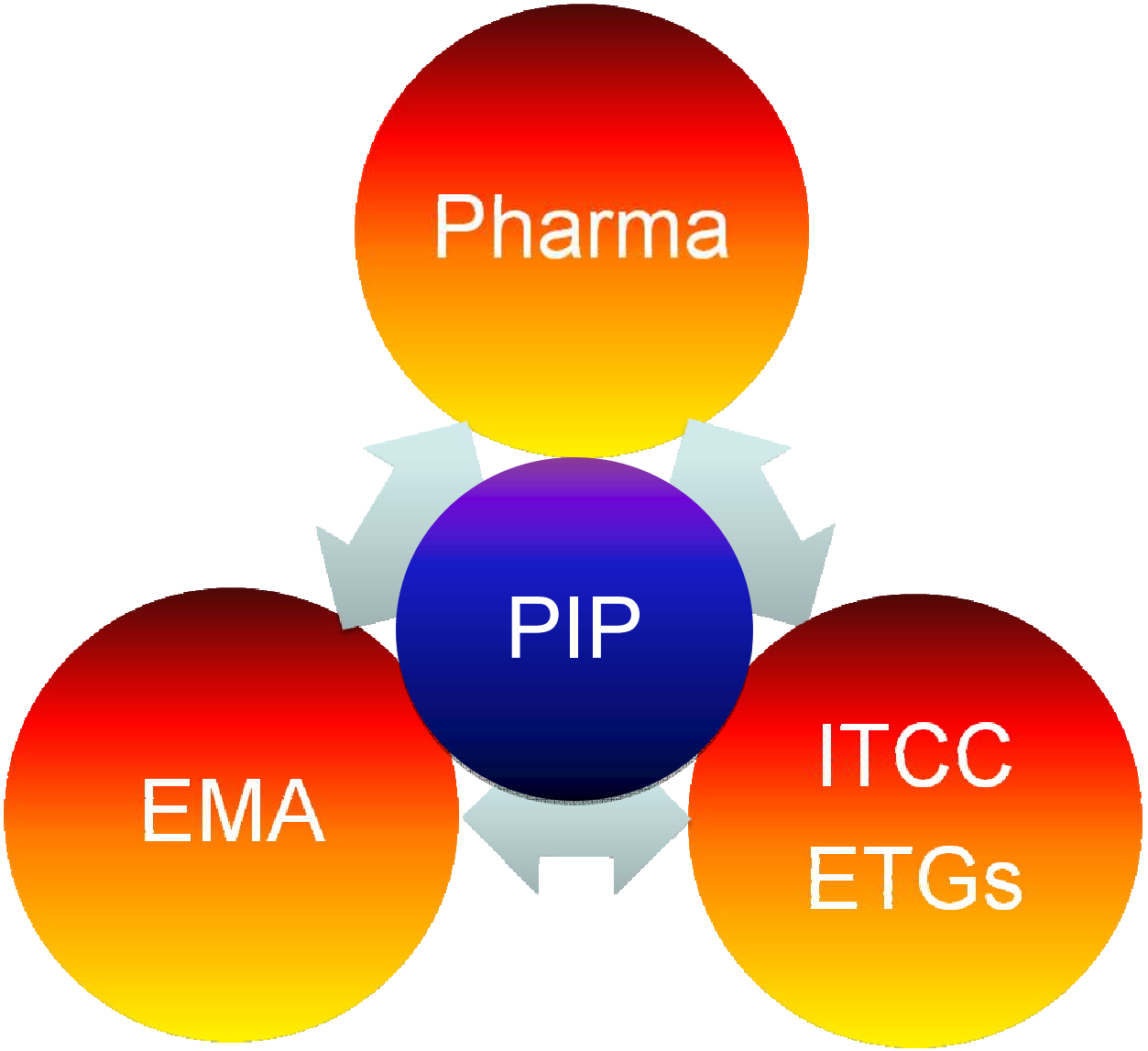
PIP in oncology : Current Situation in EU

a drug driven process from a regulatory perspective



ETG = European Tumour Groups

PIP in oncology : Proposal



Conclusion:
Improved Access to new drugs

- Still extremely limited in EU
- An urgent need to make the Paediatric Medicine Regulation a success
- Proposal: to WORK together DIFFERENTLY
  - Define a drug development strategy for each disease (before any drug is concerned) - Guidance
  - Consider paediatric drug development as an R&D issue
  - Facilitate a dialogue geared toward cooperation and information sharing between Regulators, Academia and Industry
  - Define a global EU strategy and a « business model » for paediatric anticancer drug development through strong public/private partnerships