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Current Perspective

Will children with cancer benefit from the new European Paediatric Medicines Regulation?

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ABSTRACT

In December 2000, the European Parliament voted a resolution addressing the need for better medicines for children in Europe and asking the Commission to prepare a new regulation. Members of the European Parliament considered that there was indeed a health issue to be addressed and resolved at the EU level. Six years later, the EU regulation was published and entered into force on January the 26th, 2007. This European law is going to impact significantly access to new drugs for children with cancer. By considerably changing the landscape of drug development for children, the law will provide an opportunity to make further progress in the cure and quality of cure of children with cancer, at a time when truly innovative and effective anticancer drugs are becoming available. However, there are some risks and pitfalls that need to be anticipated and controlled in order to ensure that children will eventually benefit from the European initiative.

1. Introduction

In December 2000, the European Parliament voted a resolution addressing the need for better medicines for children in Europe and asking the Commission to prepare a new regulation. Members of the European Parliament considered that there was indeed a health issue to be addressed and resolved at the EU level. Indeed, 50% to 75% of medicines used in children have not been studied adequately in the paediatric population to provide appropriate labelling information.[1]

Six years later, the EU regulation was published and entered into force on January the 26th, 2007.[2] This is a regulation which signifies that it applies, in its present form, in each member state on the very day of its publication, without any need for implementation in national laws, as opposed to a European Directive, such as the Clinical Trial Directive (European Union Directive 2001/20/EC).[3]

This European law is going to have a significant impact on access to new drugs for children with cancer. By considerably changing the landscape of drug development for children, the law will provide an opportunity to make further progress in the cure and quality of cure of children with cancer, at a time when truly innovative and effective anticancer drugs are becoming available. However, there are some risks that need to be anticipated and controlled in order to ensure that children will eventually benefit from this European initiative.

2. Pharmaceutical companies are incited to study drugs in children

The goal of the European Paediatric Medicines Regulation is:

- To improve the health of children in Europe by:
  - Increasing high quality research into medicines for children

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- Promoting the development and authorisation of such medicines
- Improving information on medicines designed for children

- While avoiding unnecessary studies in children.
- And not delaying the authorisation of medicines for adults.

The Members of the European Parliament wanted this research, mainly drug development, to be directed towards children's needs.

According to the law, the paediatric issue must be addressed appropriately in the submission file of any drug when it is submitted for the first marketing authorisation or a variation thereof. This covers all type of drugs, including biologicals. Pharmaceutical companies are asked to prepare and submit a Paediatric Investigation Plan (PIP) at the end of phase I or pharmacological studies. Once approved by the European Medicines Agency (EMEA), the PIP should be undertaken to generate paediatric data that will eventually be submitted in the application.

A waiver can be granted for paediatric development:

- for medicines intended to treat conditions that occur exclusively in adults (e.g. a waiver will be issued for a drug designed to treat Alzheimer's disease),
- for medicines that may be unsafe or ineffective,
- for medicines that do not offer a significant therapeutic benefit and/or fulfil a therapeutic need in children.

In addition, deferral of the initiation or completion of the PIP (some or all of the measures) can be authorised when it is appropriate to conduct the first studies in adults or when paediatric studies will take longer to conduct than studies in adults.

The pharmaceutical companies obtain a reward – a 6-month extension of the duration of the patent or the supplementary protection certificate. A compound is usually protected for 7 years during which no generic compound can be marketed and the pharmaceutical company can thus enjoy returns on its investments. The 6-month extension is a substantial reward for most of the drugs since the extended market exclusivity represents significant benefits when the drug is sold throughout Europe.

The need for additional paediatric information on off-patent medicines has also been addressed by the regulation. Indeed, some of these old drugs, used daily in paediatrics, have not been adequately tested in the paediatric population. A Paediatric Use Marketing Authorisation (PUMA) can be granted for off-patent medicine that provides additional information according to the needs identified by the EMEA. In addition, the 7th European Framework Programme launched specific calls for proposals to support studies on those old drugs which are unlikely to be funded by large pharmaceutical companies.

3. Children with cancer urgently need new drug development

Cancer is a rare disease in children. Paediatric malignancies account for 1% of all cancers in humans. In Europe, 15,000 children are diagnosed with cancer each year. During the last 50 years, the outcome of children with cancer has dramatically improved. More than 75% of patients are cured with multimodality treatments, with cytotoxic anticancer drugs playing a major role. This was achieved essentially through prospective clinical studies performed by paediatric oncology networks and cooperative groups because pharmaceutical companies were not committed to developing their drugs in the paediatric population. Those academia-driven studies used commercially available drugs to treat adult cancers. Standard treatments and recommendations for the use of anticancer drugs in children (dose, schedule, safety profile, efficacy, pharmacokinetics,...) have been established by the paediatric oncology community, while 50% of those drugs are not fully authorised to be put on the market according to the pharmaceutical rules that apply to pharmaceutical companies.[4] The challenge of the next decade will be to improve the quality of cure of long-term survivors of childhood cancers.

Despite the high cure rates achieved with current multimodality treatments, cancer remains the leading cause of death due to disease in children over the age of 1 year. Cancer is still a health issue. Safe and effective innovative therapies are urgently needed to improve cure rates and the quality of cure in children. The development of high-throughput technologies has increased our knowledge on tumour biology and paved the way for identifying targets for the design of anticancer compounds with new mechanisms of action, new profiles of antitumour activity as well as new toxicity profiles. Recent examples in adult oncology such as antiangiogenic compounds in kidney cancer[5] and in hepatocarcinoma,[6] two notoriously refractory diseases, raise hopes for children with relapsed and/or refractory malignancies. There has therefore been a dramatic increase in the number of new anticancer compounds under development worldwide, and oncology has become the first area for drug development.[7]

Considering this growing field of oncology drugs, it is a societal issue to make new drugs available as soon as possible to children with cancer and to develop them in accordance with good clinical practice and ethical requirements. The most refractory paediatric diseases with an urgent therapeutic need are high-risk neuroblastoma, high-risk leukaemias, metastatic soft tissue and bone sarcomas, malignant brain tumours (accounting for 20% of all paediatric cancers), in particular brain stem tumours, and other metastatic diseases.

More than 75% of anticancer drugs currently used in paediatric cancer chemotherapy are old off-patent drugs. There are numerous trials, including phase III and pharmacological studies, that recommend the safe use of the great majority of these drugs, even though their summary of product characteristics (SmPC) does not systematically provide paediatric information.

Three transversal needs in the field of off-patent anticancer drugs:

- *Better use of chemotherapy in infants*
  There is a lack of pharmacological information enabling one to recommend most of the drugs used during the

first year of age when major changes occur in physiological processes (maturation of the glomerular filtration rate, of metabolizing enzymes,...) that are involved in drug disposition. Protocols propose empirical dose reduction according to age. However, there is a risk of toxicity and/or a lack of efficacy in this very young population of children who must receive chemotherapy.[8]

- *Age-appropriate formulations for oral anticancer drugs*
  Oral chemotherapy is being used to treat several paediatric malignancies. Available oral formulations (capsules or pills) are not suitable for young children. On a daily basis, pieces of capsules are crushed and mixed with food or liquid, with the risk of not accurately administering the prescribed dose and without any knowledge about stability and bioavailability. Among these drugs are: temozolomide, retinoic acid, 6 mercaptopurine, etoposide, cyclophosphamide, and methotrexate.
- *Epidemiology of long-term sequelae*
  During the last 50 years, the use of chemotherapy in paediatric oncology has increased dramatically and contributed significantly to the currently improved outcomes of children with cancer, with more than 75% of patients being cured.[9] At the same time, long-term toxicity (e.g. anthracycline-induced cardiac toxicity, second malignancies and myelodysplasia, ifosfamide-related renal toxicity, fertility issues) has emerged and significantly alters the quality of life of paediatric cancer survivors.There is a need for epidemiological and pharmaco-epidemiological studies to identify and evaluate long-term toxicities in sufficiently large cohorts and to serve as a basis for intervention on those toxicities (awareness, adapted care) and for prevention trials. This can be achieved through the development of specific compounds to protect normal tissues and through de-escalation trials replacing toxic drugs by new active and less toxic compounds.

4. The European paediatric oncology community is ready to develop new drugs

During the last 40 years, a network for clinical research in paediatric oncology, stemming from national cooperative paediatric oncology groups, has developed in Europe.[10] SIOP Europe tumour groups and the IBFM group run phase III trials in malignant solid tumours and leukaemias, respectively, as well as late phase II trials in relapses. They represent around 250 clinical centres. There is an outstanding track record of major European phase III clinical trials that have contributed to improving outcomes in children with cancer and to developing standard care. However, access to innovative compounds developed in adults by pharmaceutical companies has been extremely poor in Europe during the last 20 years, and was always delayed when it finally occurred. This is in significant contrast with the US where NCI-granted programmes have provided easy access to new compounds for patients and the paediatric oncology community during the last decades.

Following the European resolution on paediatric medicines, it was anticipated that access to new drugs for children with cancer will eventually be improved and the need for specific expertise in the field of early drug development was identified. The European consortium for Innovative Therapies for Children with Cancer (ITCC) was created in 2003 to develop new drugs, both at the preclinical and clinical levels, in malignant solid tumours and leukaemias. The ITCC runs a comprehensive biology-driven early drug development programme for children with cancer. This network identifies relevant biological targets using a large biobank of tumour samples, evaluates anticancer drugs in relevant *in vitro* and *in vivo* paediatric tumour models and runs phase I and early phase II trials through a network of 36 clinical investigation centres in six member states (France, the United Kingdom, the Netherlands, Italy, Germany, Austria).[11] The ITCC serves as a European one-stop-shop for pharmaceutical companies to gain access to expertise and patients, in order to develop their paediatric investigation plans.

Joint programs have been established between the ITCC and the major European paediatric tumour groups in order to be able to develop full paediatric investigation plans. Indeed, improved cancer cure in children will stem from a better knowledge of paediatric cancer biology and from new targeted compounds combined with existing treatments or replacing ineffective therapies. A biology-driven drug development strategy needs to be established for each disease in order to prioritise compounds and to increase the likelihood of success. Being able to run a full drug development programme, from phase I to phase III, in line with patient needs, through a well integrated network of existing European paediatric tumour groups is of crucial importance for addressing the challenge of improving cure and the quality of cure in children with cancer. Finally, the medical community is still committed to running academia-sponsored trials, although it is difficult to do so with the 2001 European Directive on Clinical Trials.[10,12]

Despite the resolution of the European Parliament, paediatric development of new anticancer drugs has remained extremely limited until now. Since December 2000, when the resolution for better medicines for children was voted for by the European Parliament, 29 anticancer drugs have been authorised by the EMEA in 21 different diseases or conditions (Table 1). Only seven of those diseases or conditions occur in both adults and children. Only six drugs have a full paediatric indication, mainly a haematological disease or condition. Among the 23 drugs without a paediatric indication, six are indicated in a disease occurring both in adults and children, namely malignant gliomas, PH+ chronic myeloid leukaemia, non Hodgkin lymphoma and advanced soft sarcomas (even though there are some histopathological and genetic differences between adult and paediatric sarcomas). For the remaining 17 drugs indicated for a disease occurring in adults only, 12 definitely have a strong biological and/or preclinical rationale that warrants their evaluation in children. Overall, 18 of the 23 drugs (78%), which stated in their summary of product characteristics that there are no data allowing them to recommend their use in children, should be evaluated in the paediatric population. In addition, since January 2007,

Table 1 – Medicines that have been centrally approved by EMEA for the treatment of a malignant disease or condition between January 1st, 2001 and July 31st, 2008 (source: EMEA website).

	International non proprietary name	Commercial name	Mechanism of action/class	Company	Paediatric indication	Adult disease	Same disease in children	Rationale for other diseases in children
2008	Thalidomide	Thalidomide Pharmion	Immunosuppressant	Pharmion	No	Multiple myeloma	No	Yes
2007	Nelarabine	Atriance	Prodrug of araG	GSK	Yes	T-cell acute lymphoblastic leukaemia	Yes	–
						T-cell lymphoblastic lymphoma	Yes	–
	5-Aminolevulinic hydrochloride	Gliolan	Photodynamic agent	Medac	No	Malignant glioma	Yes	–
	Nilotinib	Tasigna	Tyrosine kinase inhibitor: bcr-abl	Novartis	No	Ph+ chronic myelogenous leukaemia	Yes	–
	Lenalidomide	Revlimid	Anti-angiogenic and immunomodulating agent	Celgene	No	Multiple myeloma	No	Yes
	Trabectedin	Yondelis	Cytotoxic agent	Pharmamar	No	Advanced soft tissue sarcoma	Yes	Yes
	Temsirolismus	Torisel	mTOR inhibitor	Wyeth	No	Advanced renal cell carcinoma	No	Yes
	Panitumumab	Vectibix	Monoclonal antibody anti-EGFR	Amgen	No	EGFR expressing metastatic colorectal carcinoma with non-mutated (wild-type) KRAS	No	Yes
2006	Dasatinib	Sprycel	Multikinase inhibitor: bcd-abl, src family, c-kit, ephrin, PDGFRb	BMS	No	PH+ chronic myeloid leukaemia	Yes	–
						Ph+ acute lymphoblastic leukaemia	Yes	–
	Sunitinib	Sutent	Multikinase inhibitor: PDGFRa, PDGFRb, VEGFR1, VEGFR2, VEGFR3, kit, FMS-like tyrosine kinase 3, CSF-1R, RET	Pfizer	No	Malignant gastrointestinal stromal tumour	No	Yes
						Renal cell carcinoma	No	
	Sorafenib	Nexavar	Multikinase inhibitor	BMS	No	Hepatocellular carcinoma	No	Yes
						Renal cell carcinoma	No	
	Clofarabine	Evoltra	Puric nucleoside antimetaloite	Genzyme Europe	Yes	Acute lymphoblastic leukaemia in paediatric patients	Yes	–
2005	Erlotinib	Tarceva	Anti-EGFr tyrosine kinase inhibitor	Novartis	No	Non-small cell lung cancer	No	Yes
						Pancreatic cancer	No	
2004	Bevacizumab	Avastin	Anti-VEGF monoclonal antibody	Genentech	No	Carcinoma of the colon or rectum	No	Yes
						Breast cancer	No	
						Non-small cell lung cancer	No	
						Renal cell cancer	No	

	Pemetrexed	Alimta	Thymidylate synthase inhibitor	Lilly	No	Malignant pleural mesothelioma	No	Yes
						Non-small cell lung cancer	No	
	Cetuximab	Erbitux	Anti-EGFR monoclonal antibody	Merck	No	Epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer	No	Yes
						Squamous cell cancer of the head and neck	No	
	Cladribine	Litak	Puric nucleoside analogue	Lipomed	No	Hairy cell leukaemia	No	No
	Bortezomib	Velcade	Proteasome inhibitor	Janssen-Cilag International	No	Multiple myeloma	No	Yes
	Mitotane	Lysodren	Cytotoxique	Laboratoire HRA Pharma	Yes	Adrenal cortical carcinoma	Yes	–
2003	Fulvestrant	Faslodex	Antioestrogen - oestrogen receptor antagonist	Astra Zeneca	No	Oestrogen receptor positive breast cancer	No	No
	Ibritumomab tiuxetan	Zevalin	Anti CD20 monoclonal antibody	Biogen Idec	No	CD20+ follicular B-cell non-Hodgkin's lymphoma	Yes	–
2002	Arsenic trioxide	Trisenox	Arsenic	Cephalon Europe	Yes	Acute promyelocytic leukaemia	Yes	–
2001	Capecitabine	Xeloda	Cytotoxic, prodrug of 5-fluorouracile	Roche	No	Colorectal cancer	No	No
					No	Gastric cancer	No	
					No	Breast cancer	No	
	Busulfan	Busilvex	Alkylating agent	Pierre-Fabre	Yes	Conditioning regimen prior to conventional haematopoietic progenitor cell transplantation	Yes	–
	Cytarabine liposome	Depocyte	Cytotoxic agent	Mundipharma	No	Lymphomatous meningits	Yes	
	Imatinib mesilate	Glivec	Tyrosine kinase inhibitor: bcr-abl, c-KIT, PGFRa, PDGFRb,	Novartis	Yes	Ph+ chronic myeloid leukaemia	Yes	No
						Ph+ acute lymphoblastic leukaemia	Yes	
						Malignant gastrointestinal stromal tumour	No	
	Temoporfin	Foscan	Photosensitising agent	Biditec Pharma	No	Head and neck squamous cell carcinoma	No	No
	Alemtuzumab	MabCampath	Anti CD52 monoclonal antibody	Genzyme Europe	No	B-cell chronic lymphocytic leukaemia	No	Yes
	Bexarotene	Targretin	Retinoid	Eisai Ltd	No	Cutaneous T Cell Lymphoma	No	No

no significant increase has been observed in the number of new anticancer drugs under development for children with cancer in Europe.

5. Parents and parent organisations are committed

When standard treatments fail, parents demand new treatments and access to new drugs. The ability to run early drug trials with innovative therapies is significantly greater in the US compared to Europe, even though the European Paediatric Oncology community has expended major efforts during the last 5 years. Information is largely available on the internet and parents are often ready to cross the ocean to offer their child access to a new drug and hope. This is deleterious for the patient, the parents and the entire family, and often very costly. New drugs should be made easily available at an early stage of their development for children in Europe, through clinical trials respecting GCP in order to avoid uncontrolled use of new compounds.

Partnerships have been established between parent organisations and paediatric oncologists. The involvement of the International Confederation of Childhood Cancer Parent Organisations (ICCCPO) is well known, advocating for access to high quality standard care and innovation for every child,[10] and they are committed to clinical research. ICCCPO is a full partner of the ITCC network and works in collaboration with several European tumour groups. They review information and consent packages in clinical trials and, in some cases, review protocols. They also help explain why clinical research is needed in order to continue to improve the cure rate and the quality of cure.

6. EMEA plays a central role in the implementation of the regulation

At the end of phase I or pharmacological studies, the pharmaceutical companies have to submit a PIP that considers the needs of children when developing a drug and proposes a development plan. The EMEA Paediatric Committee was set up in July 2007 and is composed of 27 members representing all fields of interest in paediatric medicine, in addition to representatives from all EU member states. Parent representatives and healthcare professionals are full members as well. The Paediatric Committee assesses paediatric investigation plans and provides advice. All information is made public on the EMEA website.

In addition, specific measures have been or are in the process of being implemented by the EMEA:

- an inventory of paediatric needs
- the creation of a network of paediatric networks to facilitate the conduct of high-quality paediatric clinical studies
- the preparation of guidelines

Since July 2007, the Paediatric Committee has evaluated nearly 400 PIPs and requests for waivers corresponding to more than 600 different indications. About 25% were in the field of paediatric oncology. Several of these PIPs concerned compounds that have been authorised for marketing since 2000 (Table 2).

The EMEA had anticipated specific needs. In June 2004, a note for guidance on the evaluation of anticancer compounds in children was published.[12] In addition, the EMEA recently created a Task Force in Paediatric Oncology to address the issues raised by the new regulation in the field and to streamline drug development in accordance with paediatric needs.

7. The US paediatric medicine regulatory initiative is a success

Since 1997, the US has developed two types of programme.[14] The Best Pharmaceuticals for Children Act is a programme inciting pharmaceutical companies to voluntarily provide information on the use of drugs in children. Through the 1998 Paediatric Rule, which was followed by the Paediatric Research Equity Act in 2003, the FDA mandates sponsors to study drugs in children.

In 1997 the Paediatric Exclusivity, a 5-year programme under the Best Pharmaceuticals for Children Act, aimed at providing information for medicines used in children. According to this regulation, the FDA issues a formal written request to the product sponsor. A sponsor can voluntarily make a proposal and submit data from studies. The study results do not have to demonstrate efficacy in the paediatric population in order for a product to qualify for the 6 months of additional exclusivity. Studies with negative results are considered informative and may have important safety consequences.[15] This US regulation, unlike the European regulation, is seeking credible information and not a formal paediatric indication.

This was a successful regulation (source: FDA website). As of February 2009, 360 written requests have been issued including 40 for oncology products. Altogether, 159 drugs have been granted exclusivity, and their paediatric labelling was changed. The following oncology drugs have been granted exclusivity: busulfan, carboplatin, clofarabine, fludarabine, gemcitabine, imatinib, irinotecan, oxaliplatin, temozolomide and vinorelbine. The programme was renewed in 2002 and 2007. Of interest, none of the targeted compounds approved by the EMEA since 2001 have been issued a written request to date.

In 1998, a companion programme, named the Paediatric Rule (and further continued in the Paediatric Research Equity Act), mandated paediatric studies if adult and paediatric indications were the same and if the product would be used in more than 50,000 children or if it would represent a therapeutic advance.[16] Considering the public health issue of cancer in children, the FDA established a specific Paediatric Oncology Advisory Committee that established principles and made specific recommendations for linking adult and paediatric diseases. So far, this programme was not successful for oncology because no anticancer drug fell within the Paediatric Research Equity Act.

Table 2 – Oncology products (antiemetic compounds excluded) with an approved paediatric investigation plan or waiver, as of March 1st 2009 (source: EMEA website).

Product name	Decision date	Applicant	PIP indication	Waiver
Everolimus	11/12/2007	Novartis Europharm Limited		Renal cell carcinoma and pancreatic neuroendocrine tumour
Recombinant L-Asparaginase	01/02/2008	Medac Gesellschaft für klinische Spezialpräparate	Acute lymphoblastic leukaemia, lymphoblastic lymphoma	
Panobinostat lactate salt	01/02/2008	Novartis Europharm Limited		Cutaneous T-cell lymphoma
Docetaxel	16/05/2008	Aventis Pharma SA	Nasopharyngeal carcinoma	Nasopharyngeal carcinoma: Preterm newborn infants and term newborn infants (0–27 d) for the concentrate and solvent for solution for infusion for intravenous route Breast cancer, Non-small cell lung cancer, Prostate cancer, Head and Neck cancer, Gastric cancer
Arzoxifene	23/05/2008	Eli Lilly and Company Ltd.		Postmenopausal osteoporosis, breast carcinoma
Adenovirus-mediated herpes simplex virus-thymidine kinase gene	23/05/2008	Ark Therapeutics Ltd.	High-grade glioma	High-grade glioma: Children aged 0 to less than 1 month for the concentrate for solution for injection for intracerebral use
Everolimus	15/08/2008	Novartis Europharm Ltd.		Carcinoid tumours
Bortezomib	14/09/2008	Janssen-Cilag International NV		Mantle cell lymphoma
Bevacizumab	01/10/2008	Roche Registration Ltd.	Rhabdomyosarcoma	Rhabdomyosarcoma:Preterm newborn infants, term newborn infants (from birth to less than 28 days) and infants (from 28 days to less than 6 months)
			Non-rhabdomyosarcoma soft tissue sarcoma	Non-rhabdomyosarcoma soft tissue sarcoma:Preterm newborn infants, term newborn infants (from birth to less than 28 days) and infants (from 28 days to less than 6 months)
Chimeric murine-human anti interleukin 6 monoclonal antibody	14/10/2008	Centocor B.V.		Castleman's disease
Ipilimumab	03/11/2008	Bristol-Myers Squibb International Corporation	Solid malignant tumours	
Vandetanib	03/11/2008	AstraZeneca AB	Medullary thyroid carcinoma	Medullary thyroid carcinoma:Children from birth to less than 5 years for tablet for oral use
Lenalidomide	06/01/2009	Celgene Europe Limited		Myelodysplastic Syndrome

8. The EU is funding research and development of off-patent medicines and basic science in paediatric malignancies

The European Regulation identified the need to improve the use of off-patent medicines and created a specific instrument, the PUMA, to provide children with better and age-appropriate off-patent medicines. As these compounds are in the public domain and of no pecuniary interest to the pharmaceutical companies, the members of the European Parliament identified the need for funding by the European Commission. In the 7th Framework Programme, the European Commission has already launched two calls entitled: 'adapting off-patent medicines to the specific needs of paediatric populations'. Public and public/private consortia are currently funded to study drugs in agreement with the priority list established by the EMEA. Several paediatric oncology projects are ongoing.

In addition, the European Commission had previously funded several basic and translational research projects in its 5th and 6th Framework Programmes that focussed on several paediatric malignancies.

9. What are the risks and pitfalls?

Everything is in place to improve early access to innovative therapies for children with cancer, to introduce them into standard care and to launch the long-term follow-up programmes which will anticipate long-term sequelae and adverse effects.

The European Paediatric Medicine Regulation has created a unique situation where all stakeholders, namely the paediatric oncology community, parents, regulatory bodies and pharmaceutical companies, have common and specific interests in developing better pharmaceuticals for children, provided they build strong and win-win partnerships. This represents a unique opportunity to speed up therapeutic research for children with cancer at a time when so many new drugs are under development and translational research is creating hopeful prospects for better cures in children with cancer.

One must realise that the European regulation created a new framework where each stakeholder is on a learning curve. Indeed, this is the first time that the EMEA approves drug development plans before data are submitted for a marketing authorisation and, until recently, paediatric expertise at the EMEA was rare considering the low number of applications that previously concerned paediatric use. Paediatric malignancies represent a brand new area for pharmaceutical companies and they have yet to acquire expertise in this field. Generating clinical and pharmacological data for the purpose of drug approval is quite a new activity for paediatric oncologists who are experts in the field of academic clinical trials for the validation of therapeutic strategies but poorly versed in the field of drug development. In addition, paediatric oncologists and pharmaceutical companies are not used to working together.

Two years after the regulation entered into force, and after nearly 400 PIPs have been evaluated by the EMEA Paediatric Committee, it is time to ask the following questions:

- will children with cancer benefit from the regulation?
- what are the anticipated risks and pitfalls that should be addressed in a timely fashion to make the regulation a success for patients?

Most of the risks identified in oncology, as well as proposed solutions, also apply to other paediatric diseases such as HIV infection or epilepsy.

10. Drug prioritisation must be a major objective

There are around 2000 new compounds under evaluation each year, including more than 500 anticancer compounds. Current surveys indicate that only 5% of oncology drugs under clinical development will eventually be authorised and marketed (the so-called attrition rate).[7] In addition, the oncology portfolio of pharmaceutical companies is expected to continue to grow significantly, while efforts are being made to improve the success rate of drug development through the early use of biomarkers in order to identify patients who are likely to benefit.

In this situation, a key objective for all stakeholders (paediatric oncologists, parents and patients, pharmaceutical companies and regulatory bodies) is the selection of compounds that need to be studied in children.

Prioritising compounds that are likely to be active in paediatric diseases is a major issue that deals with:

- *ethics*, because prioritising the drugs that are most likely to be active and avoiding those likely to be ineffective is an ethical issue where the paediatric population is concerned – a question of rapid access to new drugs that will save lives
- *science*, because those developments should be solid and scientifically based in order to ensure the best possible progress for patients and to avoid initiatives that could be considered as exclusively commercial
- *feasibility* of development, especially when the drugs concern a disease in a limited or rare population of children (which is a very frequent situation)
- *cost*, because resources, either from public bodies or private companies, are necessarily limited.

The EU Parliament strongly committed the EU Commission and the EMEA to consider paediatric needs in order to identify drugs that should be developed in children.

11. Therapeutic needs should be adequately defined in order to prioritise compounds

A PIP evaluation process is started by a pharmaceutical company when it intends to submit a file for the first marketing authorisation or a variation for an approved drug. There is therefore a risk that drugs intended for evaluation in children will be considered one after the other based on the timing of the submission to the EMEA. The level of scientifically-based priority for one compound *versus* another may be missed. This is of crucial importance when similar compounds

(e.g. monoclonal antibodies) with the same mechanism of action are developed by several pharmaceutical companies at the same time. It is also extremely important when different types of therapeutic interventions on several biological pathways can be considered for a given paediatric malignancy. It is crucial that the decision coincides with the therapeutic needs and that the priority is best identified in collaboration with the paediatric oncology community.

Therapeutic needs should be adequately defined on the basis of disease biology, the state of the art of the therapeutic strategies and current or planned academic therapeutic research programmes.

In oncology, the vast majority of new compounds are targeted, i.e. one or several cellular proteins or genes are known to be the drug target(s) with pharmacodynamic evidence that hitting the target(s) with the compound alters the phenotype of cancer cells that die, stop growing or enter differentiation. In addition, early drug trials, the so-called Proof of Concept trials, aim at demonstrating that the drug inhibits its target in humans and at defining the dose, blood drug concentration yielding such inhibition, its extent and duration and the optimal administration schedule. There is already some evidence that targeted drugs may have effects that are off-targets (or off the known target).[17]

Prioritising drugs for development in children will be strengthened through the identification of relevant targets and pathways for a given malignancy and/or through preclinical evidence of the activity of a compound against relevant tumour models. There is a clear need to fund research on tumour biology at the European level and to network the internationally recognised and expert European research teams which have dedicated their work to paediatric malignancies. Such an effort should be supported, at the EU level, through public funding of research networks and programmes, and through public/private partnerships.

In addition, there is a need to define guidelines for the pharmacodynamic and preclinical evaluation of anticancer compounds in paediatric malignancies. Preclinical testing has already been considered in the paediatric addendum to the note of guidance for the evaluation of anticancer drugs in humans.[13] However, new paradigms for targeted drug discovery and development have emerged compared to those of cytotoxic compounds. There is a need to update this guidance and to take into account the biology of the diseases for drug prioritisation by either pharmaceutical companies, academia or regulatory bodies.

The definition of therapeutic needs should be further based on state of the art knowledge on the disease, on the opinion of experts and on therapeutic strategies that are being evaluated in a given disease. Indeed, it takes 5 to 7 years to complete a phase III randomised trial in a 'not-so-rare' paediatric malignancy in Europe. It is essential to prioritise compounds and to identify the main questions to raise in order to ensure that progress will be achieved for the benefit of children. In addition, prioritising compounds from drug companies based on the disease and the needs defined by paediatric oncologists will significantly increase the feasibility of drug development plans in the paediatric networks.

The EMEA has already issued a list of paediatric needs for off-patent drugs and marketed drugs.[18] Now, there is a need to define the main relevant targets and pathways in paediatric malignancies, even though this is an area of continually expanding knowledge. In addition, a new drug development strategy should be established for the main paediatric malignancies taking into account first-line treatment but also subsequent treatments (2nd, 3rd, or even more lines) in the event of relapse. Thus, one would define the treatment administered in each of these situations and one could also propose new therapies, either in phase II or in phase I. The ITCC is currently establishing strategies and programmes through strong collaboration with the European tumour committees conducting phase III trials on the different paediatric tumours under the umbrella of SIOP Europe in order to introduce innovative drugs for the care of children with cancer in the future.

12. There are major concerns about the use of waivers in oncology

The waiver is an important process used to prioritise drugs and thus to regulate the number of drugs that will enter the paediatric research area for evaluation during the next 20 years. In accordance with the Paediatric Regulation, the Paediatric Committee adopted on July 14th, 2008, a list of conditions that occur exclusively in adult populations (http://www.emea.europa.eu/htms/human/paediatrics/class-waivers.htm), such as adenocarcinoma of the pancreas, adenocarcinoma of the colon and rectum, bladder carcinoma or breast cancer. Twenty of the 35 conditions listed are related to oncology. All classes of medicinal products intended to treat these conditions do not, therefore, require a PIP.

Based on this list of malignancies that do not occur in children, pharmaceutical companies may be tempted to systematically ask for a waiver for most of their compounds under development in adult malignancies. Compounds of potential interest to children could be missed.

A waiver in oncology should not be issued on the histological type of disease, but rather on the mechanism of action. Breast cancer does not occur in children and it is therefore appropriately included among the EMEA list of waivers. This means that the companies should not be asked to develop a drug for breast cancer in children. However, this should not mean that a drug developed in breast cancer will not be tested in paediatric cancers.

Indeed, the same drugs that cure women with breast cancer also cure children with cancer. Cyclophosphamide and anthracyclines are major drugs used in standard chemotherapy of breast cancer but those drugs also contribute to the cure of many children with malignancies such as leukaemias, neuroblastomas, lymphomas and sarcomas. Antiangiogenic drugs are active in breast cancer, as well as in other cancers in adults. They are likely to be active in paediatric malignancies as well.

In addition, a targeted therapy for breast cancer may be effective in paediatric malignancies if the target is present or altered in those diseases and its role has been functionally validated. Indeed, druggable cancer targets are often, even though not systematically, relevant for several histological types of adult cancer. After the first registration in one cancer, pharmaceutical companies often explore their drugs in other types of cancers. Paediatric malignancies are likely to harbour

several targets that are relevant in adult cancers, despite their different histologies. They should not be overlooked during drug development on purely histological grounds.

Thus, the decision to grant a waiver should be based on the mechanism of action and on the biological/preclinical evaluation rather than on the histological type of cancer.

13. Standards for drug development need to be adapted to the paediatric oncology setting

Each paediatric malignancy is a rare disease according to the European definition. In order to conduct a phase III study, hundreds of patients are required in a pan-European trial for several years, often more than 5 years. A case in point is the ongoing European phase III trial in high-risk neuroblastoma which began in 2002 and is scheduled to close in 2010. Thus, a randomised phase III trial will not be possible for each compound of interest that will need to be evaluated during the next 20 years. The situation is even more difficult for rare paediatric tumours that require international trials. Approval or conditional approval in a paediatric malignancy should also be considered without phase III data.

Demonstrating relevant antitumour activity in a recurrent paediatric malignancy may lead to regulatory approval. However, some of the gold standards of anticancer drug development designs used in adults are not feasible in the paediatric population. For example, a randomised clinical trial in relapsing patients comparing a new drug versus the best supportive care (i.e. no anticancer treatment) is unacceptable to parents. In addition, overall survival cannot be a systematic primary endpoint for oncology drug approval in the paediatric setting for ethical and pragmatic reasons. Tumour response and event-free survival along with an appropriate risk management programme and evaluation should be considered as alternative endpoints.

Thus, gold standards for drug development plans should take into account the specificities of the paediatric population. In addition, there is a need to innovate the design and methodology of new drug trials in order to speed up development. A focus on better extrapolation from adults to children would certainly contribute to this goal.

14. Development of innovative anticancer therapies for children should be funded both by private companies and public bodies

It is unlikely that paediatric needs will be covered exclusively by Pharma-sponsored trials. Cancer accounts for more than 60 different diseases in children. Biology, genomics and targeted therapies are currently differentiating frequent adult cancers into several subtypes, which will tend to include fewer and fewer patients. For example, K-ras mutated colon cancer is resistant to anti-EGFR monoclonal antibody-based therapy.[19] Patients with K-ras mutated colon cancer account for about 30% of patients with colon cancer. This is a new subgroup of patients defined according to tumour biology. Breast cancer is currently being subdivided into four different subgroups (basal-like, Her-2 positive, luminal A, luminal B)[20] and molecular classification is likely to further impact the selection of adjuvant chemotherapy for each patient.[21] Ongoing clinical research exploring biology-driven treatments and aiming at personalised medicines will eventually provide a specific treatment for each subtype of breast cancer. The same situation is occurring in paediatric malignancies. There is no longer one type of medulloblastoma (a malignant tumour of the cerebellum) but at least five as defined by genetic profiles, pathway signature and clinicopathological features.[22,23] They will probably be treated with significantly different drugs in the future.

In such a complex situation, it is unlikely that pharmaceutical companies will devote substantial resources to paediatric cancers, especially at a time when major changes are taking place in the pharmaceutical industry as a result of the global economic crisis. For most new drugs, pharmaceutical companies will limit their investments to the approved PIPs that are unlikely to cover all the needs in a dynamic way. Introducing innovative therapies to treat children with cancer should partly remain or be a non commercial issue that requires funding from public bodies (Europe and member states) and charities.

This is exactly the current situation in the United States. The National Cancer Institute funds the Children's Oncology group, a large and unique network for clinical research in paediatric oncology, that includes a consortium running phase I trials. New drugs are provided by pharmaceutical companies to the NCI and the Cancer Therapy Evaluation Programme (CTEP) sets up their evaluation in children. This has been running for years and explains why many new anticancer compounds have been easily accessible in phase I for children in the US, while during the same time, access to those compounds was extremely difficult and limited in Europe. Furthermore, 3 years ago, the NCI funded a large Preclinical Paediatric Testing Programme, named the PPTP, to prioritise anticancer drugs provided by pharmaceutical companies for their development in children.[24]

This shows that a dynamic drug development programme for children with cancer requires commitment on the part of the pharmaceutical companies as well as public investments to properly address the challenge, even in the new framework that has been created by the Paediatric Medicines Regulations in the US and Europe.

15. Need for a global strategy at the European level

Finally, a global strategy needs to be established in Europe to address the challenge of paediatric cancers in children, the number one killer among diseases. Consider the following possible scenario:

- Early drug development (phase I and II, randomised phase II trials, single and combined agents) would be run by pharmaceutical companies in cooperation with dedicated cooperative groups, through PIPs that are based on the relevance of the mechanism of action of the compound for paediatric malignancies (even though they are different from adult diseases) and on preclinical evaluation.

- This might lead to approval or conditional approval for compounds with an interesting benefit-risk ratio.
- Further evaluation in the phase III setting would be run by cooperative groups in large academia-sponsored clinical trials co-funded by pharmaceutical companies and public bodies. The choice of compounds to be introduced would be based on a biological rationale and on data from phase II trials testing single and combined agents. This would mean that not all new drugs approved in phase II would be evaluated in phase III.
- In such a situation, the strategy for the development and introduction of new compounds in the treatment of a given paediatric malignancy could be submitted to the Paediatric Committee for scientific advice.
- In addition, the cooperative groups would be in charge of setting up prospective cohorts of patients receiving new drugs in order to anticipate and study long-term sequelae that may occur in adult survivors of a paediatric cancer or children who will be cured of a childhood malignancy. Currently, 1 out of 850 adults are in such a situation in Europe. Many paediatric oncology centres follow up their patients for a long time, and long-term survivor programmes are being developed in several European member states.

Such an approach would require strengthening the European structure for clinical research in paediatric oncology. This could be done by creating and funding a network of existing clinical research groups such as the ITCC, the SIOP Europe tumour groups and the IBFM, to facilitate the implementation of such an agenda in all European member states. This will require commitment on the part of pharmaceutical companies to establish public/private partnerships and to devote resources to paediatric oncology. Funding of basic biology research and preclinical evaluation by both pharmaceutical companies and Europe would be crucial and best invested in a network of the major labs in Europe in the field. The need for Europe and member states to fund paediatric research is highlighted by the public health issue that cancer represents in children. Charity organisations may be keen to support such a comprehensive programme from basic research to paediatric cancer care that is conducted through a well integrated and coordinated European network.

16. Conclusion

The new European Paediatric Medicines Regulation has created a new landscape for paediatric research in Europe. This is a major change and opportunity for paediatric patients. Children with cancer will benefit but only if there is a real partnership between all stakeholders: paediatric oncologists, parents and patients, pharmaceutical companies and regulatory bodies. In addition, funding by both public bodies and private companies is needed, as well as support by charities.

Conflict of interest statement

Gilles Vassal is an expert at EMEA and at the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) and provided expertise to Novartis, Lilly, Pfizer, Pharmamar, Pierre Fabre Oncology, Protherics, Roche and Sanofi-Aventis.

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