Challenges in prescribing drugs for children with cancer

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Paediatric oncology has achieved high cure rates despite the limited availability of drugs that have been specifically studied for use in children with cancer. Efficacy of these drugs has received more attention than their safety, but permanent side-effects in growing children need to be considered. An absence of pharmacokinetic data, dose-defining studies, schedules defined by age, and appropriate formulations can lead to underdosing or overdosing in specific age groups, resulting in a potential lack of benefit, development of resistance, and increased adverse drug reactions. These major clinical concerns have promoted initiatives in Europe since 2003 regarding the need for a Paediatric Regulation, aimed at improving the risk–benefit ratio of such drugs in children and providing the legal framework to overcome the limitations of the past. However, to undertake the appropriate studies of these drugs in this setting, financial support is essential. Europe is now showing its commitment to overcome the present difficulties of drug prescribing for children with cancer by introducing measures that will encourage new public–private partnerships. All those involved, including researchers, paediatric oncologists, learned societies, regulatory agencies, national agencies, and pharmaceutical companies, need to become more familiar with the opportunities opened up by the new regulation, which is aimed at providing an increased cooperation between researchers and drug developers for the benefit of children.

Introduction

Successful use of chemotherapy in children with cancer started in the 1960s with drugs such as vincristine, mercaptopurine, and methotrexate. Paediatric oncologists continued to use the armamentarium of drugs developed for adult cancers and, nowadays, about 75% of newly diagnosed children with cancer are expected to be cured (figure 1).[1] This success story has been achieved through collaborative, mainly non-commercial, clinical trials and improvements in supportive care. However, few formal studies have taken place on the pharmacology of these drugs in children, and even fewer trials sponsored by drug companies have aimed to show the antitumour efficacy of these drugs against cancers specific to childhood in order to support a licensed indication. Currently, in both Europe and the USA, an estimated 80% or more of drugs used to treat children with cancer do not have information for paediatric use in their product licence and are, thus, used off-label.[2,3] However, less than 15% of drugs approved for adults with cancer and less than 50% of those commonly used have a role in paediatric oncology.

Figure 1: **Children receiving cancer treatment at the University of Modena and Reggio Emilia, Modena, Italy**

When using such drugs in children, potential acute and chronic effects should take into account changes during the developmental stages from infancy to adulthood. Physiological and psychological changes might also occur due to the effect of treatments that inhibit the growth of tissues and organs (eg, radiation and certain drugs).[4] Therefore, a new EU Paediatric Regulation has been formed to fulfil equal treatment opportunities for children as for adults and to substantiate an ethical change in the balance between risk and benefit for assessing the use of drugs in children.[5,6] However, the barriers to undertaking proper research on children's drugs are long standing and include: the cost of studies compared with the size of the potential market; difficulties in trial design (eg, small numbers of eligible patients and lack of appropriate age-matched controls); long approval processes and increases in the time taken to complete studies in children compared with in adults; and the unique and complex ethical issues surrounding research on children and assessment of risk–benefit in those who cannot provide consent for themselves. Paediatric clinical trials of new drugs are often started many years after the drugs were tested in adults and involve testing at arbitrary doses and schedules on the basis of scaled down versions of those used in adults. By this time the drugs are already off-patent and the financial incentive for the pharmaceutical company to be involved in this phase of development will have lapsed.[7] For oral drugs, a formulation suitable for very young children who are unable to swallow tablets or capsules is often unavailable. This unavailability means clinicians have had to improvise the administration of such drugs to these children, with unknown pharmacokinetic consequences. Finally, although clinical

trialists in childhood cancer have a wide experience of the efficacy and early safety of many of the older chemotherapy drugs in children, this experience has not been used to improve product labelling or specific paediatric indications for these older drugs. During the past few years, the regulatory authorities in both Europe and the USA have taken steps to mandate paediatric studies for new drugs and to provide incentives to the pharmaceutical industry for developing paediatric indications and formulations, where relevant, for older drugs. The challenge now is to ensure this new legislation is used effectively to study relevant drugs in children.

European initiatives, developed since 2003, led to the Paediatric Regulation, which came into effect on Jan 26, 2007. This regulation is aimed at providing better drugs for children by increasing the amount of high-quality ethical research done in children and by ensuring the availability of authorised paediatric drugs and proper information on their uses. All these objectives are intended to be achieved without the undertaking of unnecessary paediatric studies and without delaying authorisation of the drugs for adult use. The Task Force in Europe for Drug Development for the Young (TEDDY) project and societies, such as the International Society for Paediatric Oncology–Europe (SIOP–E), intend to aid this initiative together. This paper deals with the issues encountered in the management of children with cancer, the barriers to overcome, and the solutions we can foresee.

Central issue of clinical research

Experimental data for cancer treatment are derived mainly from efficacy trials that are designed by collaborative groups with the main aim of improving survival for a particular type of cancer. Even when these trials are of good quality, they are not always done with a view to submit the data to the Regulatory Authorities, leading to many drugs being used off-label, especially in the paediatric population. Despite the efforts of cancer specialists and paediatric oncologists, very few studies have been sponsored by industry or included in the marketing authorisation documentation.

The need to undertake appropriate clinical trials for registration studies in children was taken into consideration in the context of the European Directive EC/2001/20 on Good Clinical Practice,[8] in which prominence is given to the ethics involving inclusion of children in experimental populations. The Directive states that clinical research needs to be done at the highest ethical level with use of appropriate methods after obtainment of informed consent, and should avoid discomfort to the child. The role of paediatric experts is emphasised and their internal or external inclusion in the Ethics Committee is recommended for the proper review of paediatric clinical-trial protocols. Unfortunately, despite implementation of this Directive in 2004, few member states of the European Union have established Ethics Committees with specific paediatric expertise. Despite the existence of 900 Ethics Committees between the 27 member states of Europe, only Finland, Netherlands, and the Slovak Republic have established committees specifically devoted to minors.[9] Although the Directive aims to improve the reliability of reporting of research by specifying the standards and reporting requirements for clinical trials, the responsibilities of the research sponsor have been greatly increased, which has led to increased bureaucracy and expense without noticeable improvements in safety. Academic researchers funded by grants no longer have the resources to undertake the number of clinical trials they would have done previously. For example, the European Organization for Research and Treatment of Cancer reported that the number of new trials it opened decreased from 19 in 2004 to seven in 2005, with a third fewer patients enrolled, an increase in trial cost (up to 85%), and double the insurance costs (from €70 million to €140 million).[10–12] The concerns of academic researchers encouraged the debate on aiding clinical trials undertaken by non-commercial organisations. The outcome of this debate is awaited. Meanwhile, some member states have encouraged changes by introducing regulatory measures[13,14] (eg, the Italian law on not-for-profit clinical trials, December, 2004) aimed at encouraging not-for-profit clinical trials without industrial sponsors and recognising their important scientific role for improving clinical knowledge.

Because most of the drugs used in childhood cancer are off-label, they automatically fall under the definition of an investigational medicinal product with the requirement for full pharmacovigilance. This definition is certainly commendable, although it is too early to lead to any noticeable improvements in patient safety for off-patent drugs with which paediatric oncologists have a long experience.

Although data from the non-commercial trials might be collected in a form suitable for use by regulatory authorities, without the support of an industrial partner interested in registering a paediatric indication, the data will not be used to improve labelling of drugs for paediatric use. The EU Paediatric Regulation[5,6] provides a non-mandatory tool, namely a new type of marketing authorisation called Paediatric Use Marketing Authorisation (PUMA), which covers therapeutic indications relevant for use in the paediatric population, as well as appropriate formulations. The regulation is aimed to promote partnership between academia and the commercial sector to develop the necessary knowledge of off-patent substances currently used off-label in children with cancer. However, if this method proves to be insufficient, then regulatory agencies might need to find additional ways to promote and support the necessary studies. Until recently, a work-sharing project (an agreement on data exchange between national and european [ie, European Agency for the Evaluation of

Medicinal Products; EMEA] regulatory agencies and the US Food and Drug Administration) existed for the assessment of paediatric data acting under the Head of Medicines Agencies, whereby specific dossiers were compiled, which included paediatric information generated outside Europe and which considered whether such information was leading to a requirement for changes to the paediatric information in the Summary of Product Characteristics (SmPC).[15] Recently, EMEA took over the full responsibility for this assessment. Therefore, nowadays, the SmPC is proposed by the applicant and needs to be approved by the regulatory agency (EMEA) for centralised procedure applications or national regulatory agencies for the application of national and mutual recognition procedures. Moreover, according to the new regulation, national regulatory authorities in member states, which approve drugs for human use, will assume more responsibility, because they can now update the SmPC and package leaflet on the basis of all the existing studies they have knowledge of and, thus, can vary the marketing authorisation accordingly. Currently, this procedure relies on study data submitted to the regulatory authorities, which do not represent the entirety of paediatric data generated by non-commercial trials. In keeping with the aims of the regulation to avoid duplicate and unnecessary studies in children, further discussions at a legislative or regulatory level should occur, on how such data could contribute to paediatric authorisation for medicinal products that are already authorised for adults. Thus, consideration of all the available data on the use of a drug in the paediatric population is imperative, as is the consideration of data derived from non-commercial clinical trials.

In view of the fact that anticancer drug development is a complex process, the favouring of interactions between industry, academia, government regulatory bodies, patient advocacy groups, and other stakeholders is important. An academic consortium known as Innovative Therapies for Children with Cancer has been established between France, the UK, Netherlands, Germany, and Italy to provide a link with industry in order to accelerate preclinical and early clinical assessment of new anticancer drugs in children. This consortium has already opened early-phase clinical trials in partnership with industrial support and has built a network of European research laboratories to coordinate preclinical assessment of new drugs in specific childhood cancers. Full industrial sponsorship of clinical trials of emerging new drugs will undoubtedly be aided by the new Paediatric Regulation, provided that the necessary funding for these trials will be made available.

Role of paediatric pharmacovigilance

Very few studies of drugs in children have done an assessment of dose, schedule, and formulation by age; instead, most clinical trials have focused on antitumour efficacy with limited data collection on side-effects. Phase III trials of older chemotherapy drugs have made fairly arbitrary recommendations for dose modification by age or weight, on the basis of each trial group's own experience.[16,17] These recommendations might lead to underdosing or overdosing in some age groups, with the risk of no efficacy, the development of drug resistance, or an increased incidence of adverse drug reactions (ADRs).[18] The latter might be due not only to inappropriate dose or schedule in children, but might also be compounded by age-related differences in organ maturation, drug metabolism, or susceptibility of a target organ to an ADR, depending on its state of maturation.

The pharmacokinetic and pharmacodynamic data of a compound can be different across different age ranges—eg, adolescents seem to be especially susceptible to avascular necrosis of bone, a side-effect of dexamethasone, which is used in the treatment of leukaemia,[19–21] whereas the side-effect of hepatic veno-occlusive disease from dactinomycin is believed to be common in very young children.[22,23] However, the rarity of some ADRs means that pharmacogenomic variation cannot be excluded as a susceptibility factor. Indeed, the fact that in 40 years of use only one substantial pharmacokinetic study of dactinomycin in children has been done, which was published in 2005, is remarkable.[24] Appropriate assessment of drug toxicity and pharmacovigilance are needed, because safety issues can arise throughout the history of a drug from preclinical screening through to clinical trials and after the drug is marketed. Although serious ADRs are rare, they represent the fourth leading cause of death in hospitalised patients in the USA, a position not far behind cancer, and have no significant difference according to age.[25] Therefore, better methods of predicting safety in the paediatric population are needed and we should cease to rely on extrapolation from adult studies.

Furthermore, sample sizes in phase I and II trials involving any age group are usually low and even in phase III trials sample-size calculations are nearly always based on efficacy assumptions. Such sample sizes can restrict the ability to record anything other than common reactions. Given these limitations, every opportunity should be taken to record as much information as possible from the occurrence of an ADR, and, because nearly all treatment schedules in paediatric oncology incorporate drug combinations, the direct link to individual drugs should be considered. The introduction of the Paediatric Directive, mandating pharmacovigilance, will hopefully lead to better data collection on ADRs, albeit with greatly increased bureaucracy. However, properly designed pharmacokinetic studies in children of some of the older drugs are still needed, as are such studies for the newer drugs. Awareness of the recently approved guidelines on paediatric pharmacovigilance[26] and the new regulation, which support both spontaneous reports and active data collection, will hopefully lead to increased confidence for use of a specific drug in children when no dose or schedule is provided in the SmPC.

Active substance	Indications for off-label use in children	Specific priorities	Age group*
Dactinomycin	Rhabdomyosarcoma, Ewing's sarcoma	Pharmacokinetics, safety	..
Carboplatin	Neuroblastoma, low-grade glioma, Wilms' tumour, hepatoblastoma, medulloblastoma, osteosarcoma, germ-cell tumour	Pharmacokinetics, safety, efficacy	<2 years
Cisplatin	Neuroblastoma, low-grade glioma, Wilms' tumour, hepatoblastoma, medulloblastoma, osteosarcoma, germ-cell tumour	Pharmacokinetics, safety, efficacy	>6 months
Cladribine	Acute myeloid leukaemia, chronic lymphoblastic leukaemia, hairy-cell leukaemia	Pharmacokinetics, safety, efficacy	..
Cyclophosphamide	Acute lymphoblastic leukaemia, acute myeloid leukaemia, non-Hodgkin lymphoma, Hodgkin's disease, neuroblastoma, rhabdomyosarcoma, low-grade glioma, Ewing's sarcoma, medulloblastoma, osteosarcoma, hepatoblastoma, germ-cell tumour, haemophagocytic lymphohistiocytosis, bone-marrow transplantation (conditioning regimen)	Age-appropriate formulation; pharmacokinetics	All age groups; <3 years
Cytarabine	Acute lymphoblastic leukaemia, acute myeloid leukaemia, non-Hodgkin lymphoma	Efficacy, safety	<3 years
Daunorubicin	Non-hodgkin lymphoma	Pharmacokinetics, long-term safety	..
Doxorubicin	Ewing's sarcoma, hepatoblastoma	Pharmacokinetics, long-term safety	..
Etoposide	Ewing's sarcoma, rhabdomyosarcoma, Hodgkin's disease	Pharmacokinetics, efficacy, safety	..
Etoposide	Acute lymphoblastic leukaemia, neuroblastoma, rhabdomyoscaroma, low-grade glioma, Ewing's sarcoma, Wilms' tumour, medulloblastoma, ependymoma, osteosarcoma, hepatoblastoma, germ-cell tumour, histiocytosis	Age-appropriate formulation; pharmacokinetics	All age groups; <3 years
Fludarabine	Bone-marrow transplantation (conditioning regimen)	Pharmacokinetics, safety, efficacy	..
Gemcitabine	Acute lymphoblastic leukaemia, acute myeloid leukaemia, Hodgkin's disease, rhabdomyosarcoma, Ewing's sarcoma, osteosarcoma, neuroblastoma, hepatoblastoma, Wilms' tumour, soft-tissue sarcoma	Pharmacokinetics, safety, efficacy	..
Idarubicin	Acute myeloid leukaemia	Pharmacokinetics, long-term safety	..
Ifosfamide	Acute lymphoblastic leukaemia, non-Hodgkin lymphoma, Hodgkin's disease, rhabdomyosarcoma, Wilms' tumour, Ewing's sarcoma, osteosarcoma, germ-cell tumour	Pharmacokinetics, efficacy, safety (and long-term safety)	..
Lomustine	Labelled paediatric use	Age-appropriate formulation	..
Mercaptopurine	Labelled paediatric use	Age-appropriate formulation	..
Methotrexate	Labelled paediatric use	Age-appropriate formulation	..
Mitoxantrone	Acute myeloid leukaemia	Pharmacokinetics, long-term safety	..
Retinoids	Labelled paediatric use	Age-appropriate formulation	..
Temozolomide	Labelled paediatric use	Age-appropriate formulation; Pharmacokinetics, safety, efficacy	All age groups; <3 years
Tioguanine	Labelled paediatric use	Age-appropriate formulation	..
Thiotepa	Bone-marrow transplantation (conditioning regimen) in medulloblastoma, germ-cell tumour	Pharmacokinetics, efficacy, safety	<12 years
Topotecan	Refractory solid tumours	Pharmacokinetics, efficacy, safety	..
Vinblastine	Langerhans-cell tumour	Pharmacokinetics, efficacy, safety	..
Vincristine	Low-grade glioma, medulloblastoma, ependymoma	Pharmacokinetics, efficacy, safety	..
Vindesine	Non-Hodgkin lymphoma	Pharmacokinetics, efficacy, safety	..
Vinorelbine	Labelled paediatric use	Age appropriate formulation	..

*Data required for specific age group according to EMEA[34]

Table 1: **Specific priorities for studies into off-patent medicinal products for children with cancer (Paediatric Use Marketing Authorisation as marketing authorisation requirement)**

Active substance*	Indications for off-label use in children	Specific priorities	Age group†
Alemtuzumab	Chronic lymphoblastic leukaemia	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Arsenic trioxide	Acute promyelocytic leukemia	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	< 5 years
Bevacizumab	Metastatic colorectal cancer	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Bortezomib	Refractory solid tumours, relapsed acute lymphoblastic leukaemia	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Capecitabine	Colorectal cancer and metastatic colorectal cancer	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Cetuximab	Metastatic colorectal cancer	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Erlotinib	Refractory solid tumours, brain tumour	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Ibritumomab	CD20+ refractory lymphoproliferative disorders	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Imatinib	Philadelphia-chromosome-positive acute lymphoblastic leukaemia	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<2 years
Liposomal doxorubicin	Refractory solid tumours, anthracycline cardiac failure prevention	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Pegylated liposomal doxorubicin	Refractory solid tumours, anthracycline cardiac failure prevention	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Mitotane	Advanced, unresectable adrenal-cortical carcinoma	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Pegylated filgrastim	Neutropenia and febrile neutropenia in patients treated with cytotoxic chemotherapy	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Rituximab	CD20+ refractory lymphoproliferative disorders	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Trastuzumab	Sarcomas	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years
Zoledronic acid	Skeletal-related events in patients with advanced malignancies involving bone, tumour-induced hypercalcaemia	Pharmacokinetics, safety, long-term safety, efficacy, age-appropriate formulation	<18 years

*EMEA list of 34 substances approved over the past 10 years. †Data required for specific age group according to EMEA[34]

Table 2: **Specific priorities for studies on off-label patented drugs for children with cancer (Paediatric Investigation Plan as marketing authorisation requirement)**

Current situation and future perspectives

Children in Europe represent more than 20% of the European population, with about 100 million people aged less than 19 years. According to the Automated Childhood Cancer Information System database[27,28] and EUROCARE studies[29,30] the efficacy of treatments that are developed for children with cancer is good and the failure of treatment to control disease still remains the main cause of death in childhood cancer rather than the toxic effects of treatment.[31] Nevertheless, no firm conclusions can be drawn from the published work about the percentage of survivors with permanent late effects and the incidence of these effects according to the tumour treatment strategy, cancer type, and single-organ involvement.[32] Therefore, a reasonable concern still exists about serious long-term side-effects, acute, toxic, treatment-related deaths, and life-threatening morbidity, as well as poor survival in children due to underdosing.[4] Most chemotherapeutic drugs are off-patent and are, therefore, no longer protected by an Intellectual Property Right and, hence, have no obvious sponsors for the needed clinical trials. European initiative to promote specific clinical trials, which fall within the priority list for studies into off-patent paediatric drugs,[33,34] is welcome (table 1). Such studies will be funded competitively under the FP7 Health-Research Community Program and, although not obligatory, are likely to contribute to the development of PUMAs. In this context, a note should be made that this initiative only applies to off-label drugs that have no paediatric indication included in the therapeutic-indication part of the SmPC, even though there might be paediatric dosing recommendations or other paediatric documentation provided. Furthermore, due to the plethora of new anticancer drugs developed for adults in recent years, combined with the limited number of children with cancer, the research community needs to consider how best to prioritise these new drugs for development in the paediatric population. This consideration should include in-patent substances, such as drugs already approved by the EMEA during the past 10 years, which are covered by a patent, but might still be used off-label in children (table 2).

Finally, the new generation of biologically targeted drugs developed for adult cancers should also be extended to childhood cancers—eg, STI571[35] (a specific inhibitor of a tyrosine kinase, which has been shown to cause cancer-cell death in a substantial number of patients, thereby giving rise to a better prognosis in Philadelphia-chromosome-positive acute lymphoblastic leukaemia) and PKC412 (a potent FLT3 inhibitor that has caused cell death in several in-vitro models and in phase I and II studies of adults with acute myeloid leukaemia).[36] These new drugs might offer survival advantages for some childhood cancers that have a bad prognosis. Of greater importance is their possible ability to act as a substitute for some of the older drugs that have known risks of permanent side-effects, such as the anthracyclines and platinum compounds. To test either of these hypotheses, appropriate clinical trials will need to be undertaken, even for rare tumours that might affect as few as two patients per year in a country the size of Great Britain.[37] Clearly, such studies would need to be done across Europe (or even worldwide) if they are to be feasible in a reasonable time scale.

Therefore, the first priority is to maintain the current good cancer survival rates by ensuring market availability of the most effective drugs proven up to now, while

increasing the number of these drugs that have specific marketing authorisation for children. Second, because improvements in survival are a priority for about a third of children whose tumours are refractory or show early progression or relapse, innovative drugs for specific age groups or indications need to be properly tested in children like they were in adults, incorporating pharmacodynamic analysis to aid the assessment of efficacy and toxic effects. A third priority is the need for better prevention and understanding of early and long-term toxic effects, which requires both a better knowledge (in terms of dose, schedule, and formulation) of what has been used so far and the availability of new substances and strategies for improvements of both supportive treatment and long-term monitoring.[4]

The fact that risk factors for many ADRs, and in particular genetic risk factors, remain largely unknown in the postgenomic era is unacceptable. Poor risk–benefit ratios, interpatient variability, and ADRs might be genetically determined, due to inherited differences in drug metabolising enzymes, transporters, receptors, or drug targets. Such information has been available for a limited number of drugs, including mercaptopurine and irinotecan, where homozygotes for the low-activity variant of thiopurine methyltransferase or for the polymorphism UGT1A1 (TA7) are known to tolerate only minute doses of the relevant drug. Since the sequencing of the human genome, high expectations have been placed on the development of predictive genetic tests, which could contribute to personalised medicines. Pharmacogenomic data and resulting tests might show patients at risk of toxic effects, with the potential for early dose adjustment or enhanced monitoring, and might allow better prediction of responders to improve patient selection for trials of targeted drugs. However, so far, the promise of pharmacogenomic testing has exceeded the evidence for its cost-effective clinical use or the ability to predict patients truly at risk, even in adults.[25]

Effects of the new Paediatric Regulation

Thanks to the Paediatric Regulation, safety and efficacy studies in the paediatric population will soon become mandatory for any drug likely to be used to treat children for which a new marketing authorisation is requested, as well as incentives for off-patent drugs.[5,6,38] The timelines of the implementation of this regulation are shown in table 3. Submittal of an agreed Paediatric Investigation Plan (PIP) for all innovative drugs that are currently unauthorised for use in children and application for a new marketing authorisation will now become compulsory. This rule will also apply to patented drugs that need a change in their marketing authorisation. The PIP is a research and development programme aimed at ensuring that the necessary data are generated, thereby establishing the conditions in which a drug can be authorised to treat the paediatric population. This plan is proposed by the applicant and must be approved by the Paediatric Committee at the EMEA.[5,6]

	Provision	Deadline
Products not yet authorised	Obligation for Marketing Authorisation: PIP study results; or waiver; or deferral	July 26, 2008
Products already authorised, but still covered by patent	Obligation for variation or extension of Marketing Authorisation: PIP study results; or waiver; or deferral	Jan 26, 2009
Authorised products no longer covered by patent	Voluntary PUMA: PIP study results	July 26, 2007

PIP=Paediatric Investigation Plan. PUMA=Paediatric Use Marketing Authorisation

Table 3: **Timelines for implementation of the European Paediatric Regulation**

The regulation also requires that data for long-term follow-up of ADRs are included in any clinical trials that take place. Marketing authorisation variations are especially relevant to many oncological drugs that are only authorised for use in adults, but which are frequently used in children. The possibility to extend the indication to paediatrics can be an attractive prospect for industries, and the rewards include 6-months' extension of the supplementary protection certificate and 2-years' additional market exclusivity for drugs for rare diseases.

For off-patent drugs, the regulation provides a non-mandatory, new type of marketing authorisation called PUMA, which covers clinical indications relevant for use in the paediatric population, as well as appropriate formulations. Rewards for obtaining this marketing authorisation are data and marketing protection (10 years) and community funding for studies (Research Framework Programmes) and other incentives by member states. A PUMA can only be obtained if new paediatric studies are done according to a PIP that has been agreed by the Paediatric Committee of the EMEA.

Additional pillars of the Paediatric Regulation are: establishment of a Network of Paediatric Research Networks appointed by EMEA; free paediatric scientific advice from EMEA; information tools (eg, an inventory of therapeutic needs, information on new product labelling requirements, and a public database of clinical trials); enhanced safety monitoring for marketed products concerning the obligation to include long-term follow-up of ADRs; and the requirement for postmarketing data for pharmacovigilance.

This regulation is a remarkable step forward, because, for the first time in Europe, it is a regulation that is provided by law, and provides direct economic support for paediatric clinical trials and indirect support for pharmaceutical industries. This regulation is especially applicable to paediatric oncology, where several older drugs are currently used on the basis of limited clinical evidence in the published work. In this setting, the new regulation allows authorities to request data to update product characteristics. Academics now have a good opportunity to propose a priority list of drugs to be

Search strategy and selection criteria

Data were identified by a search of PubMed using the terms "individual active substances", "children", "pharmacokinetic", "clinical trial", "adverse drug reaction", and specific names of adverse drug reactions. Papers published between 1977 and 2006 published in English were used. An overall quality assessment of 195 papers was done according to Cochrane Collaboration guidelines. Other papers were selected from reference lists of relevant articles.

assessed for paediatric use to the EMEA, which should encourage companies to submit a PIP for off-label patented substances and promote partnerships between academic researchers and companies.

Finally, due to the revision of drug legislation in Europe,[38] all new oncology drugs need to be authorised via the centralised procedure established by the EMEA and will, thus, be reviewed by the Committee for Medicinal Products for Human Use. In this context, the process of development and marketing authorisation for drugs used in oncology can be aided, thereby reducing the time taken for innovative drugs to reach the market.[39]

Conclusion

The effect of the new regulation is expected to stimulate high-quality research and provide robust information on paediatric drugs to increase the availability of such drugs to children. This regulation aims to keep ineffective treatment, incorrect dosing, and ADRs to a minimum; reduce hospitalisations and deaths; improve quality of life; and provide economic benefits. European regulatory actions are important steps to develop specific paediatric dosing recommendations at an early stage in the development process and to improve the safety of new anticancer drugs in children. Paediatric oncologists can now devise more rational methods of selecting which new drugs to develop and which new efficient trial designs to use for assessing safety and efficacy.

Academic research is called on to play a main part in this new process, because drug development cannot be undertaken exclusively by pharmaceutical companies. Responsibility for health care, research, and the development of new treatment strategies for severely ill patients needs to be shared to ensure that needs within these areas are allocated the necessary priority. European pharmaceutical companies should grab this opportunity to overcome the serious lag behind their world-wide competitors and to redress the imbalance in research and development competition by stimulating forms of cooperation in research and development via reinforced public–private partnerships.

The regulation includes funding for studies of off-patent drugs and, in the future, for the development of new drugs that have the highest need within the paediatric population. The expectation of this regulation is that it will provide the paediatric population with safe access to older drugs and early access to newer, safer, and more targeted treatments.

Conflicts of interest

The authors declared no conflicts of interest.

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