Need for change in implementation of paediatric regulation

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In June, 2013, after public consultation and a survey by the European Medicines Agency (EMA), the European Commission published its 5-year interim report on the implementation of the European paediatric medicine regulation,[1–3] which was launched on Jan 23, 2007, to provide better medicines for children. Safe and effective innovative medicines are needed to cure the 3000 children and adolescents dying of cancer every year in Europe.[4] Great anticipation was placed in the regulation to substantially increase the number of new cancer drugs for paediatric oncology.

As part of the regulation, pharmaceutical companies developing drugs had to develop and comply with paediatric investigational plans to get marketing authorisation for adults, unless they were granted a waiver by the paediatric committee of the EMA because the disease did not occur in children. To incentivise paediatric studies, companies were rewarded with a 6 month, financially beneficial, patent extension for successfully completed paediatric investigational plans.

For the **European Medical Agency website** see http://www.ema.europa.eu

The European paediatric medicine regulation has been a great advance in research for children with cancer, as shown by the increase in early clinical trials carried out by the Innovative Therapy for Children with Cancer European network during this period. However, there are still no trials for many potentially very effective drugs, and many children have no treatment options. The benefit for children with cancer could be substantially greater if the changes in implementation proposed by the EMA come into force.

For the **Innovative Therapy for Children with Cancer European network** see www.itcc-consortium.org

We analysed 28 oncology drugs approved for adult marketing authorisation in Europe since 2007.[5] 26 had a mechanism of action relevant for paediatric malignancies, but of these, 50% have been waived because the adult condition does not occur in children. We concluded—as proposed by the EMA and its paediatric committee—that the implementation of the regulation should no longer be driven by the adult disease in oncology, but should be guided by the biology of paediatric tumours and the mechanism of action for each drug. For the past 40 years, 90% of drugs successfully given to children and adolescents with cancer have been used for different cancers in adults.

In its interim report,[1] the commission acknowledged that "criticism has been voiced that the regulation will fail to ensure a breakthrough in areas of particular need, such as paediatric oncology". The authors of the report concluded that constraints and boundaries have to be taken into account and that "orphan regulation has to be considered given that, for example, all paediatric cancers are rare diseases and fall under the EU policy framework on rare diseases". Although we, and others, unequivocally support the proposal from the EMA and its paediatric committee to implement paediatric investigational plans on the basis of drug mechanism of action and to revoke the class waiver list,[6] the commission's conclusion seems to be that no change is needed in the implementation, and that the orphan drug regulation is more appropriate than is paediatric medicine regulation for the needs of children and adolescents with cancer.

We analysed the list of approved orphan medicinal products on the EMA website. As of July 16, 2013, 25 (34%) of 73 approved orphan medicinal products were oncology drugs (appendix). Three drugs had a mechanism of action that is not relevant for paediatric malignancies. Among the 22 drugs relevant for a paediatric malignancy, 15 had either a paediatric indication (eight drugs) or a paediatric investigation plan (seven drugs). Of these 15 drugs, the targeted conditions were mainly haematological malignancies that occur in both adults and children. Five drugs had a waiver based on the absence of the adult condition in children. Two drugs indicated for leukaemia and glioma had neither a paediatric investigation plan nor a waiver published. Crucially, no oncology drug has been registered for children in an indication different to that for adults, while oncology drugs represent a third of approved orphan drugs. Orphan designated oncology drugs are approved in children only if the paediatric malignancy is the same in adults, and paediatric development of these drugs is not systematic.

We conclude that the orphan drug regulation that has been in place since 2000 does not adequately cover the needs of children and adolescents with malignancies that do not occur in adults. 40 years of standard of care show that oncology drugs developed in adults are (or can be) relevant for paediatric malignancies based on their mechanism of action, even if the diseases are different. Children and adolescents with life-threatening

malignancies can greatly benefit if changes are made in the implementation of paediatric medicine regulation. We strongly support the EMA and its paediatric drug committee proposal as a matter of clinical urgency;[6] otherwise a key opportunity to improve outcomes for children and adolescents with cancer will be lost and progress delayed—a situation that is unpalatable to paediatric oncologists around Europe and unthinkable for families of children with cancer.

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Waiting for prevention in Australia

Guidelines for the management of individuals with a high risk of cancer due to an identified gene mutation or their family history include recommendations for intensive surveillance programmes and risk-reducing strategies. Although dependent on the cancer and the particular risk-reducing strategy (eg, screening colonoscopy in Lynch syndrome, and bilateral salpingo-oophorectomy in carriers of *BRCA1* or *BRCA2* mutations), adherence to the screening test or uptake of surgery results in well documented reductions in cancer incidence and mortality.[1,2] Adherence to screening is variable, but of concern, uptake of risk-reducing strategies remains low in carriers of *BRCA1* or *BRCA2* in Australia.[3,4] Potential barriers to uptake might include public hospital waiting times. With the health dollar stretched in many directions, and the scrutiny of current health-care provision under the umbrella of a newly elected Australian Government, it seems timely to look at some of the issues facing patients at high risk of developing a malignancy.

The Australian health system is both a public system (funded by the Medicare scheme, a tax-financed system available to all Australians) and a private system. Private health insurance is a voluntary option for private funding of hospital and ancillary health treatment, and it supplements Medicare funding. About 51% of Australians older than 15 years are privately insured, with the likelihood of being insured increasing with income (23% of individuals in the lowest income quintile are insured compared with 76% in the highest income quintile).[5] Anyone can use services provided in privately operated facilities, with out-of-pocket expenses dependent on whether they have insurance and their level of cover. Services in a publicly operated facility are usually associated with no or very small out-of-pocket expenses to the patient if they have the right to health care through Medicare funding. Generally, when a patient is placed on a public hospital waiting list for a procedure such as endoscopy or surgery, a clinical assessment is made of the urgency with which the patient needs the procedure. The clinical urgency categories are category one (admission within 30 days, disorders with the potential to deteriorate quickly), category two (admission within 90 days, disorders causing pain, dysfunction, or disability, but that are not likely to deteriorate quickly), and category three (admission at some time in the future: conditions causing little or no pain, dysfunction, or disability).


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Both screening endoscopy and risk-reducing surgical procedures are usually given the lowest priority on publicly funded lists, with patients potentially susceptible to long waits for their clinically recommended and cancer-risk-reducing interventions. Conversely, individuals accessing health care through private