Europe set to act over paediatric drugs

Mary Rice

Child cancer patients are routinely given drugs that have only ever been tested in adults. But developers may soon find themselves forced to extend trials to paediatric populations if they want new drugs approved in Europe.

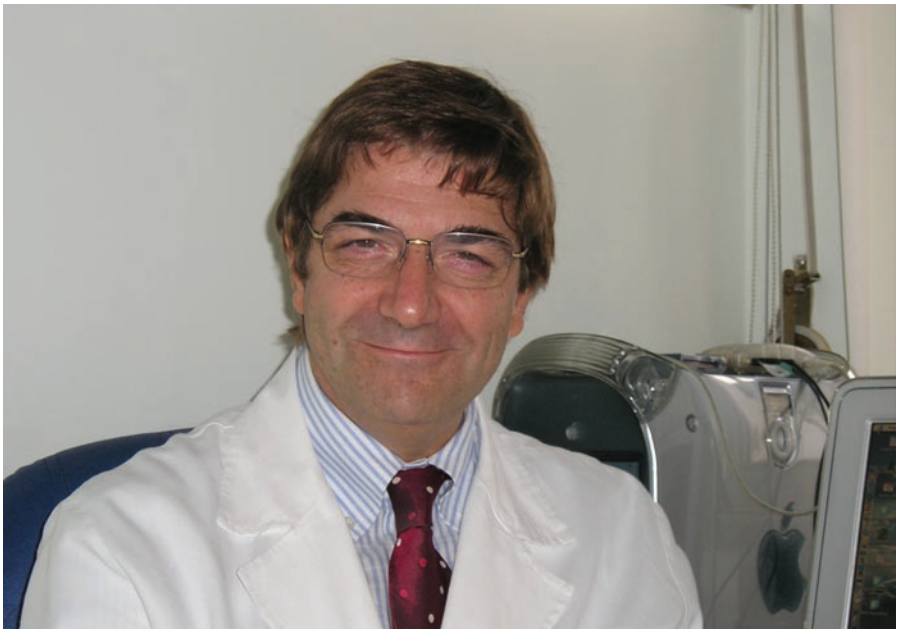
After a lengthy consultation process, at the end of September the European Commission (EC) finally published a regulation (draft legislation) aimed at tightening up marketing authorisation for paediatric medicines. The proposal follows a request from Member States to find ways to increase the number of drugs intended for use in children.

Pharmaceutical companies are reluctant to support studies to evaluate new drugs in children because the market is limited and the high costs cannot always be recouped by sales. There is also the problem of finding enough participants to have sufficient statistical power to detect small treatment effects that might be significant. Add to this the particular ethical and legal challenges involved – What constitutes an acceptable risk for a child participating in research? – and it becomes easy to see why paediatric drug research is so limited. "There needs to be a proper balance between the potential benefits and a reasonable expectation of safety," says Dr Riccardo Riccardi, Director of the Paediatric Oncology Division of the Catholic University of Rome, who is involved in international studies of new agents in paediatric oncology. "In children with cancer, clinical trials should start only after an adult phase I study has been completed and reasonable information on potential toxicity has been collected."

Consent issues are complicated too. In paediatric trials, consent is obtained by proxy from the child's parents or guardian. "Most parents, at least in Italy, are avidly seeking experimental treatments when standard therapy fails. Only a few are more reluctant to submit their child to an experimental drug or procedure than they would be if asked for their own participation. The term 'permission' rather than 'consent' may be used for parents making a decision for their child," says Riccardi.

Nearly a quarter of the EU's 480 million citizens are below 19 years of age. Yet over 50% of medicines given to children, including the newborn, have never been tested for their effects in this group. This means that the health of children may suffer, as doctors cannot be sure of the effectiveness of many medicines, nor do they know what dose is appropriate or exactly what the side-effects may be. The EC's initiative is aimed at promoting the development of badly needed paediatric drugs while ensuring that the research needed for authorisation is of the highest quality. The legislation, which has yet to pass through the Parliament and the Council of Ministers, would require pharmaceutical companies to present the results of trials involving children when requesting authorisation for new products. The effects on children would therefore be displayed on the label, and the same procedure would apply to drugs already on the market should the company wish to extend use to children. But the European legislative process is long and it seems unlikely that these measures will come into effect before 2007 at the earliest.

In exchange for the extra costs involved, companies would be given a six-month patent extension. "The paediatric exclusivity legislation introduced by the FDA in 1997, which also gives a six-month extension, has been a great success in the US and led to a considerable increase in the number of drugs available for paediatric use. I think that such an incentive would dramatically improve the situation in Europe," says Riccardi. More than 60 labels with new paediatric information for estab-



Riccardo Riccardi

lished drugs have been created in the US since the six-month extension came into force.

Statistics show that cancer is the leading cause of death in children, outside of accidents. In Europe each year about 13,000 children will develop cancer and 3,000 will die of it, yet these children's access to innovative therapy is extremely limited. From 1995 to 2002, only 2 of the 25 new drugs approved for marketing authorisation by the European Medicines Agency (EMEA) for cancer treatment were submitted with paediatric data.

"Our goal as paediatric oncologists," says Riccardi, "is to offer to European children struck by cancer newer, better, and safer compounds. Any new regulation should cover the way clinical studies are conducted in order to obtain meaningful data with maximum safety. The process should include, for example, the development of specific paediatric formulations such as the development of compounds that can be administered as a syrup."

The proposed regulation covers a number of issues, in addition to the six-month patent extension and the requirement to present paediatric trial data when applying for authorisation:

- A new expert committee will be established within EMEA to assess and agree trial design
- A new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), will be set up for off-patent medicinal products developed specifically for paediatric use
- Safer medicines and compulsory submission by the industry of existing studies in children will be required
- An EU inventory of the therapeutic needs of children and an EU network of investigators and trial centres will be set up to conduct the studies required
- Free scientific advice for the pharmaceutical industry will be provided by EMEA.

The EC proposals were subjected to an extended impact assessment carried out by external contractors and designed to estimate the economic, social and environmental impacts of the initiative. The report of the assessment found that the regulation should lead to the improvement of the health of European children through ensuring the availability of evidence-based information on paediatric medicines and hence the greater availability of authorised medicines for children.

The report found that, overall, the costs of clinical trials in children would add less than 0.5% to the costs of developing the medicines, which would be more than compensated for by the economic advantages of the six-month extension to patent protection.

"The establishment of a paediatric committee is in itself a step towards fulfilling paediatric needs as far as new medicines are concerned," says Riccardi. "The committee would be able to identify the most important needs of children and will have specific knowledge that will help to prioritise the drugs to be studied."

He warns, however, that while these changes are badly needed and their adoption should improve the present situation, EMEA is not equivalent to the FDA, and it may be more difficult to reach consensus among EU member states on specific aspects, mainly relating to existing national rules or funding. "Vigilance is called for," he concluded, "in order to ensure that the health of Europe's children does not suffer as the result of political infighting."

Sharing secrets with the FDA

Kathy Redmond

EMEA (the European Medicines Agency) and the FDA (the US Food and Drug Administration) have published a plan for implementing confidentiality arrangements agreed in principle last September. The purpose of the confidentiality agreement is to allow the regulatory agencies to share expertise, perspectives and ideas for alternative approaches to regulation. It covers both regular and ad hoc exchange of information, including information on pre-authorisation and post-authorisation applications, inspections and guidance documents, and applies to all products that fall within the remit of the EMEA and FDA.

A key part of the implementation plan is a pilot programme for companies to obtain parallel scientific advice from the two agencies, which should result in patients getting faster access to new medicines, with a particular emphasis on important breakthrough drugs. Mechanisms have been put in place for EMEA, FDA and pharmaceutical companies to exchange views on scientific issues during the development phase of new medicinal products. An exchange programme for staff of both agencies is also foreseen.

The newly published plan details the information and documents the two agencies will exchange and the process for monitoring the implementation of the confidentiality arrangements.

In a separate bid to help streamline and simplify regulatory procedures, EMEA has set up a new Committee on Herbal Medicinal Products (HMPC). The move comes in response to the Directive on Traditional Herbal Medicinal Products that came into force earlier this year. The new provisions bring in a much simpler registration procedure for herbal medicinal products, which should help harmonise the procedures and provisions concerning these products across Europe.

Genetic testing

EMEA has also starting fulfilling its newly adopted role of providing tailor-made information to patients, with a leaflet aimed at patients participating in a clinical trial that involves pharmacogenetic testing. Under the slightly obscure title of "Understanding the terminology used in pharmacogenetics", the leaflet provides patients with vital information about the risks to privacy inherent in such trials together with advice about how patients can protect their identity and safeguard their genetic information. Copies of the leaflet are available from the EMEA site: www.emea.eu.int.

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The difficult ethical, social and legal issues in human genetic testing in research and healthcare applications were also the focus of a European citizens' and stakeholders' conference convened earlier this year by the European Commission. The conference was based on a report and 25 recommendations prepared by a high-level, independent Expert Group. A report on the stakeholder conference is due shortly, but in the meantime, interested parties are invited to contribute to a debate on the 25 recommendations via a forum on the EC website: *http://europa.eu.int/comm/research/conferences/2004/genetic/index_en.htm*

ELI LILLY'S ALIMTA (pemetrexed) has been granted marketing authorisation by the European Commission for use, in combination with cisplatin, in patients diagnosed with malignant pleural mesothelioma, and, as a single agent, as second-line treatment for patients suffering from non-small-cell lung cancer.

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DRUG REGULATORS IN SEVERAL EUROPEAN countries including Germany, Sweden, Denmark, Finland, Belgium, Hungary, Portugal, and Romania have approved the extension of another Lilly product – Gemzar (gemcitabine) – for the treatment of recurrent epithelial ovarian cancer. Gemzar is already approved for the treatment of patients with pancreatic, non-small-cell lung, metastatic breast and bladder cancers.

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EUROPEAN AUTHORITIES HAVE AGREED to extend the indication for Roche's MabThera (rituximab) to first-line use in treatment of indolent non-Hodgkin's lymphoma in combination with conventional chemotherapy. The EC has also approved an extension to the dosing interval for Amgen's anti-anaemia product Aranesp (darbepoetin alfa), which can now be given once-every-three-weeks in the treatment of anaemia in adult cancer patients with non-myeloid malignancies who are receiving chemotherapy.

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SWISSMEDIC, THE SWISS DRUG REGULATOR, has approved Femara (letrozole) for the extended adjuvant treatment of postmenopausal women with hormone receptor positive or unknown early breast cancer who have received post-surgery tamoxifen therapy for five years. Switzerland is the first European country to have approved the extended adjuvant indication.

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THE MARKETING AUTHORISATION for Guilford Pharmaceuticals' GLIADEL(R) Wafer (polifeprosan 20 with carmustine implant) has been extended to use in newly-diagnosed patients with high-grade malignant glioma as an adjunct to surgery and radiation. GLIADEL(R) was previously authorised for use only in recurrent surgery for glioblastoma multiforme.

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BIOENVISION HAS SUBMITTED an application for marketing authorisation to EMEA for clofarabine for use in refractory or relapsed acute leukaemias in children.

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ROCHE HAS SUBMITTED A MARKETING authorisation application to EMEA for Tarceva (erlotinib) for the treatment of advanced non-small-cell lung cancer. A similar application has been filed with the FDA. The company has also applied to EMEA for an extension of the indication of Xeloda (capecitabine) to the adjuvant treatment of colon cancer.

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THE MERGER BETWEEN SANOFI AND AVENTIS has resulted in the birth of Sanofi-Aventis, the world's third largest pharmaceutical company. Oncology operations got off to a good start – the European authorities extended Eloxatin's (oxaliplatin's) indication to cover the adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour and Taxotere's (docetaxel's) to cover hormone-refractory prostate cancer.

NEW ORPHAN DRUGS

A number of agents with cancer indications have been designated as Orphan Medicinal Products by the European Commission. They include:

- (R,S)-3-(bromomethyl)-3-butanol-1-yl-disphosphate (Innate Pharma) for the treatment of renal cell cancer
- Porfimer sodium used with photodynamic therapy (Axcan Pharma International) for the treatment of cholangiocarcinoma
- Midostaurin (Novartis Europharm) for the treatment of acute myeloid leukaemia
- Sorafenib tosylate (Bayer Healthcare) for the treatment of renal cell carcinoma
- Anti epidermal growth factor receptor antibody h-R3 (Oncoscience) for the treatment of glioma
- 5,10-methylene-tetrahydrofolic acid (Interface International Consultancy) for the treatment of pancreatic cancer in combination with 5-fluorouracil
- Homoharringtonine (Stragen France) for the treatment of chronic myeloid leukaemia
- Recombinant human interleukin-21 (Novo Nordisk) for the treatment of renal cell cancer