In contrast to the situation concerning adults, most medicines used to treat the children of Europe have not been tested on children and are not authorised for use in children. Therefore, the health and quality of life of children in the EU countries may suffer from a lack of testing and authorisation of medicines for their use. In particular, 46% of medicines prescribed to children in hospital are either unlicensed for their age group or, if they are, have been done so off-label.1 Of the children who receive medication in hospital this figure rises to 67%,1 and in the context of intensive care up to 90% of paediatric medicines used are not licensed.2

Although there may be concerns voiced about conducting trials in the paediatric population, this has to be balanced by the ethical concerns related to giving medicines to a population in which they have not been tested and therefore their effects, positive or negative, are unknown.

The European Parliament and Council Regulation on Medicinal Products for Paediatric Use3 aims to improve the health of the children of Europe by increasing the research, development and authorisation of medicines for use in children, and as such represents a major breakthrough in paediatrics research. Its policy objectives are:

- to increase the development of medicines for use in children;
- to ensure that medicines used to treat children are subject to high-quality research;
- to ensure that medicines used to treat children are appropriately authorised for use in children;
- to improve the information available on the use of medicines in children; and
- to achieve the above while avoiding unnecessary studies in children.

Ensuring that children have access to high-quality, effective and safe medicines, accompanied by high-quality information based on robust evidence, is crucial to giving children and their doctors the ability to make informed decisions about the treatment of disease and ensuring that the chosen medicines improve health. However, the diseases suffered by children often differ considerably from those suffered by adults, and the bodies of children tolerate drugs differently from those of adults.

The dose of a medicine to treat a childhood disease cannot always be extrapolated from the adult dose: medicinal products used in the paediatric population have never been specifically studied or authorised (licensed) for use in that age group. This leaves no alternative for the prescriber than to use products off-label – i.e. the use of a product authorised for adults (that is, products that have not been tested or authorised for paediatric use) – or the use of completely unauthorised products with the associated risks of inefficacy and/or adverse reactions (side effects).

To remedy this state of affairs, new and established medicines will have to undergo research – including clinical trials in children – and pharmaceutical companies will have to obtain marketing authorisation based on the data generated. Medicines authorised for children will have to be marketed differently and clear and robust information about how and when to use the medicine will have to be available and accessible. The paediatric regulation proposes to address all of these factors through the specific policy objectives above. Within the context of the regulation, medicinal products can be broken down into three groups:

- products in development that have yet to be authorised;
- authorised products still covered by intellectual property rights (IPRs); and
- authorised products no longer covered by IPRs, i.e. off-patent.

The regulation contains a package of measures aimed at each of the above. Most apply to all, whereas others are specific to products falling into just one of the three groups listed above.

The first two of these categories involve requirements for new medicinal products and authorised medicines covered by a patent or a supplementary protection certificate (SPC). The purpose of this is to present the result of studies in children according to an agreed paediatric investigation plan at the time of marketing authorisation application or application for a new indication, novel dosage form or new route of administration.

A system of waivers will ensure that research in children is conducted only to meet the therapeutic needs of children, and a similar system of deferrals will ensure that research is carried out only when it is safe and ethical to do so. This will also ensure that the requirement for data in children will not block or delay the authorisation of medicines for other populations. For example, such studies in children may be
A study programme for off-patent medicines for children is now part of a large-scale project into a major subject or disease in paediatrics, where defining and testing potential remedies is but a part of a research and development programme.

Of major relevance to the Seventh Framework Programme (FP7) is the third category of medicines, where there is no possibility of offering extended patent protection. Therefore, a new type of marketing authorisation is proposed – the Paediatric Use Marketing Authorisation (PUMA) – together with a study programme to fund or part-fund research into the paediatric use of off-patent medicines. PUMA is specifically for off-patent medicinal products developed exclusively for use in children, and provides a vehicle for awarding the incentive of data protection. This is an IPR that can be applied to off-patent medicines to stimulate innovation by allowing their use to treat new diseases and new populations. Of course, it is weaker than patent protection as competitors could carry out their own research and development programme on the same active substance if they judge the market to be big enough. Therefore, data protection is not a guarantee of market exclusivity.

In any case, an important argument against ‘re-awarding’ market exclusivity to such products is that generics are already on the market and revoking their marketing authorisations is justified only if it is in the interest of public health, such as safety concerns. Quite simply, this means that market exclusivity is impossible in a multiproduct environment. Second, if – as has been suggested – the status of orphan medicine were to be awarded to such potentially new formulations, it would be contrary to the objective of promoting their general availability, since the orphan regulation aims to stimulate through incentives the development and authorisation of specific treatments for rare diseases. By definition, these are few in number, whereas the objective of this part of the regulation is for as many medicines on the EU market to be tested (other than generics) and authorised (including generics) for use in children and thereby to promote such availability. Therefore, data protection is considered to be the most practical option for all off-patent medicines for children even if the incentive is less when no child-specific formulation is required.

A study programme for off-patent medicines for children is now part of the FP7 and represents the other incentive anticipated by the regulation, i.e. "...Funds for research into medicinal products for the paediatric population shall be provided for in the Community budget in order to support studies relating to medicinal products or active substances not covered by a patent or a supplementary protection certificate. This is delivered through the Community Framework Programmes for Research, Technological Development and Demonstration Activities (Article 40)." It is based on a list of paediatric priorities for off-patent products devoid of commercial interest, drawn up by a group of experts in paediatrics at the European Medicines Agency (EMEA) and the Paediatric Committee (PDCO), for which studies would have to be publicly funded. Two selection criteria are applied, the first of which is conditions or disease states in terms of clinical seriousness and absence of therapeutically authorised alternatives, taking into particular account the need for neonatal treatment, where such needs are most acute. The second criterion is a demonstration of therapeutic interest from published clinical reviews, especially from previous clinical trials in children of the data, efficacy or safety of pharmacokinetics (PK). The final judgement on whether to fund research will depend on the combination of these two considerations.

The original version of this programme has been used for the Call for Proposals launched in 2007 for each of these classes by the Paediatric Committee. Overall, the proposals received as a result of this Call covered a broad range of ages listed as being high priority and some of the conditions listed. There was generally good coverage of malignant diseases, infectious diseases and neonatology, but somewhat limited attention given to a number of paediatric specialties, e.g. no proposals in ophthalmology, gastroenterology or psychiatry, and only one proposal in cardiovascular medicine. New EU Member States were significantly under-represented. Of these proposals, six were recommended to receive funding, of which three deal with oncology and one each with respiratory medicine, the needs of neonates and infectious diseases. Another Call for Proposals is proposed for September 2008.

General Observations
Some products will need full development in at least one age group, whereas others need only a complement of information followed by regulatory assessment. The cost of developing a formulation is about €750,000. In Europe, the cost of development by academic centres would be about €200,000 for a PK study, €500,000 for dose-finding work and €1.7m for efficacy and safety studies. Therefore, the limit of the EC contribution to these projects has been set at €6m per project.

A figure of €30m for the first Call for Proposals was set aside as the EC contribution for this research activity. Similar amounts may be proposed for future Calls. Of course, this does not include any additional pre-clinical development that may be required. It should also be emphasised that the entry into force of the Good Clinical Practice (GCP) Directive (EC No. 2001/20) as of May 2004 will significantly increase the cost of clinical development, as GCP requirements are labour-intensive. The extent of this is unknown to date.

The list will be updated periodically to maintain up-to-date estimates of the products. A final list of priority products will be available from the EMEA when the next Call for Proposals is launched on 3 September 2008.

Paediatric oncology merits special consideration because nearly all children with cancer have already been enrolled in numerous studies that have been published. Furthermore, broadly discussing ‘oncology’ per se does not necessarily address matters of drug development in the field where a given product’s antineoplastic activity outweighs the condition itself and will determine the combination of such drugs studied. However, as with other conditions, the lack of PK data in younger age groups and the lack of paediatric formulations are pressing. The preparation of extemporaneous formulations of highly toxic oncology products requires additional precautions over and above those needed for other pharmaceutical entities and entails additional risks to those of extemporaneous paediatric preparations in general. The needs of children under three years of age will merit special consideration.

An added feature of the forthcoming Call for Proposals is that participating centres based in countries that are neither EU Member...
Current Issues

States nor associated countries (e.g. Albania, Croatia, the former Yugoslav Republic of Macedonia, Iceland, Israel, Liechtenstein, Montenegro, Norway, Serbia, Switzerland and Turkey) will be eligible to receive funding. This will enhance co-operation between European research centres and other top-quality organisations, e.g. in North America, for the benefit of children worldwide.

Other Matters for Consideration

Additional concerns that need to be addressed include the study of data that have been collected by cohorts and registries over decades to determine the long-term effects of medicines. In the future, child-friendly formulations for existing medicinal products need to be developed, and the needs of neonates and adolescents across the spectrum of all medicines and gender differences in the metabolism of medicines need to be considered.

Stakeholders

Children, their parents and their families are the ultimate stakeholders affected by the paediatric regulation. Currently, children are denied robustly tested, authorised medicines to meet their therapeutic needs; the main objective of the paediatric regulation is to improve the health of children by ensuring an adequate supply of such medicines. Their representatives are encouraged to participate in research proposals.

Healthcare professionals such as medical doctors, paediatricians and other specialists, pharmacists, nurses and researchers will want to provide their patients with effective, safe and high-quality products, rather than take personal legal liability for the effects of the untested, unauthorised medicines that they are bound to prescribe. Health professionals are also involved in research into the effects of medicines in children and measures to increase research will influence those involved.

In much of the EU, national governments are ultimately responsible for healthcare, including medicines. They are responsible for promoting the health of their citizens and also have an economic interest in having a healthy population with low healthcare and social security needs who are able to work and generate wealth.

Other stakeholders are the authorities who regulate the pharmaceutical industry. More specifically they are responsible for the approval of clinical trials in Europe, the authorisation of medicines and manufacturing facilities, inspecting factories, laboratories, clinical trials and market authorisation holders, maintaining marketing authorisations and pharmacovigilance, which means monitoring the safety of marketed medicines, and taking action to increase benefit and reduce risk from them.

The pharmaceutical industry comprises large companies (a few that are predominantly based in the EU) and smaller companies (many more that are firmly based in the EU). Furthermore, the industry can be divided into the innovative industry, responsible for the discovery, research and development of innovative medicines, and the generics industry, which is responsible for limited research only but undertakes the manufacture of generic copies of off-patent innovative medicines.

Many generic pharmaceutical companies can be classified as small and medium-sized enterprises (SMEs), as they have fewer than 250 employees, an annual turnover not exceeding €50m and a balance sheet not exceeding €43m. This sector is of special interest to the FP7 as they represent an important part of its client base. Another important member of this category is the contract research organisation (CRO). All potential SMEs are urged to register as such with the EMEA. This will enable considerable savings to be made in the seeking of various degrees of scientific advice and inspection fees at the EMEA by reductions of up to 90% and the deferral of payments for such advice until after successful authorisation of products.

The Main Provisions for Small and Medium-sized Enterprises

A variety of incentives have been established to assist SMEs:

- administrative and procedural assistance from the SME Office at the EMEA;
- fee reductions for scientific advice (90% fee reduction) and inspections;
- fee exemptions for certain administrative services (excluding parallel distribution);
- deferral of the fee payable for an application for marketing authorisation or related inspections;
- conditional fee exemption where scientific advice is followed and a marketing authorisation application is not successful; and
- assistance with translations of the product information documents submitted in the application for marketing authorisation.

A responsible and dedicated office has been established at the EMEA for the submission of requests for designation of SME status and to answer queries. A comprehensive guide has been published giving further information.

Conclusion

Europe’s children deserve the highest standards of research and ethical protection, and these initiatives are designed to provide this. Based on the existing and considerable resources in the form of off-patent medicines, more research can now be initiated and outcomes can be directly brought ‘from bench to bedside’ in one of the first initiatives of its kind worldwide. This is already showing results in terms of a positive impact on the health and wellbeing of children, while at the same time boosting the innovative capacity of European health-related industries and businesses and promoting international collaboration.