

# **Inventory of Community and Member State rewards and incentives to support research into, and the development and availability of, medicinal products for paediatric use**

## **Background**

Regulation (EC) No. 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use (hereinafter 'the paediatric regulation') was adopted on 12<sup>th</sup> December 2006. It was published in the Official Journal of the European Communities on 27<sup>th</sup> December 2006<sup>1</sup> and entered into force on 27<sup>th</sup> January 2007.

Article 39(2) of the paediatric regulation requires Member States to communicate to the Commission detailed information concerning any measure that they have enacted to support research into, and the development and availability of, medicinal products for paediatric use. Article 39(3) requires a detailed inventory of all rewards and incentives provided by the Community and the Member States to support research into, and the development and availability of, medicinal products for paediatric use to be made publicly available. The information in this inventory is intended to be updated on a regular basis.

## **Aim of the Paediatric regulation**

This paediatric regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations. These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations. The paediatric regulation strives to achieve these objectives through a package of requirements, rewards and support measures. The key measures can be summarised as:

- the establishment of an expert paediatric committee (PDCO) within the European Medicines Agency (EMA);
- a requirement at the time of marketing authorisation applications for new medicines and certain line-extensions for certain existing medicines (generally newer ones) for data on the use of the medicine in children resulting from an agreed paediatric investigation plan;
- a system of waivers from the requirement for medicines unlikely to benefit children and a system of deferrals of the timing of the requirement to ensure medicines are tested in children only when it is safe to do so and to prevent the requirements delaying the authorisation of medicines for adults;

---

<sup>1</sup> OJ L 378, 27.12.2006

- a reward for compliance with the requirement in the form of six-months extension to the supplementary protection certificate – SPC (in effect, six-month patent extension on the active moiety);
- for orphan medicines, a reward for compliance with the requirement in the form of an additional two-years of market exclusivity added to the existing ten-years awarded under the EU orphan regulation;
- a new type of marketing authorisation, the PUMA, which allows ten-years of data protection for innovation (new studies) on off-patent products;
- measures to increase the robustness of pharmacovigilance and to maximise the impact of existing studies on medicines for children;
- an EU inventory of the therapeutic needs of children to focus research, development and authorisation of medicines;
- an EU network of investigators and trial centres to conduct the research and development required;
- a system of free scientific advice for the industry, provided by the EMEA;
- a public database of paediatric studies;
- a provision on EU funding into research leading to the development and authorisation of off-patent medicine for children.

The aim of this inventory is to collect together the measures that have been introduced both at Community level and at national level and to present this information in a transparent manner. To this end Member States have been asked to communicate details of any measures introduced or in force. In addition, information from the different services of the Commission has also been requested. This inventory is based on the information received by July 2008.

## **1. Community measures**

### **1.1 The Regulation on medicinal products for paediatric use**

The principle measure introduced by the Community is the paediatric regulation. Since the entry into force of this regulation, the EMEA, the Member States and the European Commission services have been working on its full implementation and on its operation. Details of this work at Community level can be found on the website of the EMEA<sup>2</sup> and of the Commission<sup>3</sup>.

#### *Work of the EMEA paediatric committee (PDCO)*

The PDCO held its first meeting on 4 July 2007. In its first year of operation, the PDCO performed strongly in its core activities relating to the assessment and agreement of

---

<sup>2</sup> <http://www.emea.europa.eu/htms/human/paediatrics/introduction.htm>

<sup>3</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/medchild\\_key\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/medchild_key_en.htm)

paediatric investigation plans (PIPs) and waivers. From August 2007 to July 2008, the PDCO received 233 validated applications of which 49 were requests for a full waiver for all conditions and all subsets of the paediatric population. These covered approximately 420 indications. As a result of the assessment of these applications, the PDCO adopted 71 opinions, one of them negative. 31 opinions were adopted for full waivers and 39 for PIPs. An opinion on a PIP may also contain deferrals and/or waivers for the obligation to gather clinical trials data in certain age groups of children. PDCO opinions on PIPs and waivers are transformed into EMEA decisions. The EMEA adopted decisions on 30 of the 71 opinions on PIPs and waivers. Of these, 15 were for full waivers and 15 for PIPs. Orphan medicines, which are intended for the diagnosis, treatment or prevention of rare diseases, represented 17% of the PDCO applications. For 73 % of these, an application for a PIP was submitted, and for 23 % waivers were requested.

Other highlights of the work of the PDCO include:

- A proposal, adopted by the EMEA Management Board, for an implementing strategy for the European network of paediatric research.
- A guidance document on the content and format of data to be collected by Member States on all existing uses of medicines in the paediatric population. The data collected by the Member States in accordance with this guidance should be communicated by national competent authorities to the EMEA by January 2009. The PDCO will establish an inventory of paediatric needs based on the information obtained from the survey.
- A list of class waivers for conditions that do not affect children and for which the requirement to submit a PIP can therefore be waived.
- Priority list for studies into off-patent medicines (medicines not covered by a patent in Europe) in the context of the call from the European Commission for funding through the EU's Seventh Framework Programme.

A detailed report on the first year of operation of the PDCO is available on the web<sup>4</sup>.

## **1.2 EU Framework Programmes for Research and Technological Development**

The EU's Framework Programme for Research and Technological Development provide an important vehicle for EU support into medicines for children. Various projects relating to medicines for children have been funded through the 6<sup>th</sup> Community Framework Programme. These are:

- Selecting and Validating drug targets from the human kinome for high risk paediatric cancers
- Prognosis and therapeutic targets in the "Ewing" family of tumours
- European Embryonal Tumor Pipeline
- Chimeral T cells for the Treatment of paediatric cancers

---

<sup>4</sup> <http://www.emea.europa.eu/htms/human/paediatrics/pdco.htm>

- European network to promote research into uncommon cancers in adults and children: pathology, biology and genetics of bone tumours
- Task force in Europe for drug development for the young.

Further details of these projects can be found at [Annex 1](#).

With regard to funding through the 7<sup>th</sup> Community Framework Programme, one project can be made public at this time:

- Relating expectations and needs to the participation and empowerment of children in clinical trials.

Further details of this project can also be found at [Annex 1](#).

Additionally, in the second call for proposals of the 7<sup>th</sup> Community Framework Programme fifteen proposals were received directly relating to medicines for children. These covered a broad range of ages listed as being high priority and some of the conditions listed on the Priority list for studies into off-patent medicines produced by the PDCO. Six projects have been recommended to receive funding and of these, three relate to oncology, one to bronchopulmonary dysplasia, one to pain/analgesia and one to infectious diseases.

### **1.3 EU Public Health work**

Details of the EU Public Health work are available on the European Commission website<sup>5</sup>. Projects relevant to medicines for children include:

- European Commission support to Member States in areas such as immunisation of children against vaccine-preventable diseases.
- The European Commission is developing a proposal for a Council Recommendation on childhood immunisation. The proposed Council Recommendation aims at facilitating the switch between different national childhood immunisation schedules for families with children taking up residence in another Member State, and seeking a firm political commitment from Member States to step up efforts at increasing and maintaining a very high childhood vaccination coverage for priority vaccine preventable diseases (measles, mumps, rubella, diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* b, hepatitis B). The above initiative is proposed to be part of the Commission Legislative and Work Programme 2009.
- The European Centre for Disease Prevention and Control (ECDC) which aims at strengthening Europe's defences against infectious diseases, issues scientific opinions on immunisation in general (including children's vaccination) which could affect research and availability regarding medicinal products for paediatric use.
- The European Commission is developing a Communication on rare diseases "Rare Diseases: Europe's challenges" (planned for adoption November 2008). This will include orphan drugs for rare diseases.

---

<sup>5</sup> [http://ec.europa.eu/health/index\\_en.htm](http://ec.europa.eu/health/index_en.htm)

- In November 2007, the European Commission organised a workshop on children's health which included work to promote the development of medicines for children<sup>6</sup>.

## **2. Information from Member States**

Incentives available at Community level need to be supported by complementary national initiatives, particularly in areas such as fiscal incentives and national research projects. Pursuant to Article 39(2) of the paediatric regulation, information on National measures has been received from eighteen of 27 Member States. Not all Member States had taken specific measures.

This information reflects the situation at the start of the entry into force of the regulation, and that as this information is updated, the input of Member States in this area can be expected to increase.

The information provided to the European Commission is presented according to the information received from each Member State.

### **2.1 Austria**

#### **Financial grants, bursaries, awards and incentives**

In Austria, the Federal Ministry of Health, Family and Youth granted 40.000 € to the Austrian Society for Paediatrics for the intended purpose of developing a project guide on establishing an Austrian network on studies concerning medicinal products for children and adolescents.

#### **Taxation relating to research infrastructure**

The Federal Ministry of Health, Family and Youth together with the Federal Ministry of Science and Research are currently investigating possibilities for establishing a common Austrian network for paediatric studies.

#### **Measures relating to expertise and advice**

A group of experts on medicinal products for paediatric use has been established. This group of experts shall provide the preconditions for an Austrian paediatric network, which will be able to participate in the joint European network. The aims of the group are

- to provide safe medicinal products and therapies for children
- to establish a network on paediatric studies in Austria
- to create quality-based standards for paediatric therapies
- to found a forum of experts among the Austrian paediatricians
- to ensure international synergies

---

<sup>6</sup> [http://ec.europa.eu/health/ph\\_information/implement/wp/lifestyle/ev\\_20071120\\_en.htm](http://ec.europa.eu/health/ph_information/implement/wp/lifestyle/ev_20071120_en.htm)

- to establish data-systems on the use of medicinal products for children and ongoing paediatric studies.

Scientific advice for the pharmaceutical industry can be obtained from AGES PharmMed, the agency responsible for the inspection and approval of medicinal products and medical devices in Austria.

## **2.2 Belgium**

In Belgium no specific measures have been taken at the time of reporting to support research into medicinal products for paediatric use.

Penalties on infringements of the paediatric regulation have been foreseen in a draft law which is at the moment under discussion in the Parliament.

## **2.3 Bulgaria**

### **Financial grants, bursaries, awards and incentives**

This subject is in the field of competence of Patent office of Republic of Bulgaria.

### **Taxation related measures**

The new amended national project of Law on the Medicinal Products in Human Medicines includes taxation related measures.

### **Measures targeting small and medium sized enterprises**

The new amended national project of Law on the Medicinal Products in Human Medicines includes measures targeting small and medium sized enterprises.

## **2.4 Cyprus**

The pharmaceutical industry in Cyprus is involved in the manufacturing of generic medicinal products. Clinically oriented innovative research and development in the pharmaceuticals sector is not actually performed.

### **Financial grants, bursaries, awards and incentives**

Although there are no specific provisions for paediatric research, there are a number of programs that may be utilised towards this end.

### **Ministry of Commerce, Industry and Tourism**

The Ministry of Commerce, Industry and Tourism provides grants to businesses for the purchase of new equipment and for developing technological expertise. These grants have benefited the local pharmaceutical industry at times, as part of their efforts towards technological advancement. The current scheme for the period between 2007 and 2013

sponsor's small and medium-sized enterprises (SME) on matters of equipment and technical expertise providing grants up to 400.000 Euros.

### **Cyprus Research Promotion Foundation**

The Cyprus Research Promotion Foundation is an independent establishment that promotes scientific and technological research in Cyprus. Its main measures include three packages: Measures on Health Research, Measures on SME Research and Measures Relating to the Development of Research Infrastructures.

#### **Measures on Health Research**

This scheme includes the program on "Biological Sciences-Health". The main target of this scheme is the design of high quality research in the fields of Public Health, Biomedical Sciences and Biotechnology and Food Science and Biotechnology. Grants under this scheme may be up to 160.000 Euros.

#### **SME Research**

This is a new scheme that includes the "Development of Research and Innovation in Businesses" program. The main aim of the scheme is to improve the competitiveness, viability and development of Cypriot enterprises and the creation of new work posts in research and development. Grants under this scheme may be up to 170.000 Euros.

#### **Measures Relating to the Development of Research Infrastructures.**

The aim of the scheme is to help develop research infrastructures by upgrading current infrastructures and the creation of new ones with emphasis on innovative scientific sectors. Grants under this scheme may be up to 800.000 Euros.

#### **Measures relating to research infrastructure**

The provisions of Directive 2001/20/EC are fully transposed into the national legislation of Cyprus. Sponsors and investigators may utilise the current infrastructure to conduct paediatric clinical trials.

## **2.5 Czech Republic**

### **Financial grants, bursaries, awards and incentives**

The Ministry of Health (MoH) has launched a call for proposals for the health programme of research and development of the MoH for the period of 2008-2011 including pharmacological research, focused on increase of treatment effectiveness and security and on enrichment and enhancement of the spectrum of medicines. The submitted applications are currently being evaluated.

The MoH simultaneously prepares a follow-up programme for 2009-2011 which includes not only pharmacological but also paediatric research, focused on improvement of health care for young people, new therapeutic procedures and other contributions in the field of paediatric health care provision.

## **2.6 France**

Measures introduced by the AFSSAPS (Agence Francaise de Securite Sanitaire des Produits de Sante) to encourage research into, the development of and access to medicinal products for paediatric use are provided below.

### Scientific opinions

In order to help laboratories wishing to develop medicinal products, especially for paediatric use, the AFSSAPS, assisted by experts, delivers scientific opinions on request and free of charge.

### Networks of paediatric investigators

In order to have competent paediatric investigators at its disposal, the AFSSAPS is working on the development of networks of such investigators, in particular by establishing a map of clinical test investigators specialising in this field and by preparing a training framework for investigators.

Assistance with the formalisation of a quality assurance system for these networks can also be provided by the AFSSAPS.

### Development and accessibility of medicinal products for paediatric use

The AFSSAPS has introduced controlled systems for access to medicinal products without market authorisation in France:

#### – Pre-authorisation access

The pre-authorisation access system allows medicinal products without market authorisation in France to be made available as an exception for patients with serious or rare diseases. In this connection it should be noted that a quarter of such patients are children. The AFSSAPS publishes, on its website, a list of medicinal products (updated monthly) for which it has granted pre-authorisation access. This information draws attention to a need that is not satisfied and may encourage laboratories to submit, where appropriate, applications for marketing authorisations for medicinal products for paediatric use in France.

#### – ‘Sui generis’ authorisation

Certain medicinal products for which pre-authorisation access has been granted for paediatric use are authorised in other European countries. The AFSSAPS is therefore helping to prepare a draft decree implementing Article L. 5121-9-1 of the Public Health Code (transposing Article 126a of European Directive 2004/27/EC). This provision states that where a medicinal product is authorised in another Member State but does not have a marketing authorisation in France and is not the subject of an application for pre-authorisation access currently being examined, the AFSSAPS may authorise the marketing of that medicinal product on public health grounds.



## – Hospital preparations

If a suitable proprietary medicinal product is not available, hospital pharmacies are authorised to produce their own preparations which are then declared to the AFSSAPS. Forty-four percent of such preparations are for paediatric use. The AFSSAPS subsequently considers whether or not these hospital preparations are essential and looks for proprietary medicinal products in other countries to replace them. Information is disseminated via the AFSSAPS website.

The AFSSAPS also aims to standardise and thus optimise the manufacture of hospital preparations by entering them in the national register of formulae.

### **Financial incentives**

Concessions have been granted in France for medicinal products for paediatric use in connection with the fixing of prices by the Financial Committee on Health Products (CEPS). These concessions are set out in the framework agreement concluded between the CEPS and the French Pharmaceutical Companies Association (LEEM).

This framework agreement first of all increases the fixed price guarantee from five to six years in the case of medicinal products for paediatric use for which studies have been carried out in application of a paediatric investigation plan.

The framework agreement also requires the list of paediatric needs drawn up by the AFSSAPS to be sent to the LEEM by the CEPS. This list must include new paediatric forms or validation of paediatric indications for existing presentations.

Once a medicinal product is included in the list drawn up by the Paediatric Committee within the European Medicines Agency and in the list of paediatric needs drawn up by the AFSSAPS, its manufacturer's price net of taxes must ensure a daily treatment cost level which is equal to the daily treatment cost of the medicinal product in adults.

Medicinal products for paediatric use corresponding to the list of paediatric needs also benefit from the accelerated procedure for granting reimbursement eligibility (within 180 days) applied in accordance with the rules to medicinal products bringing therapeutic progress.

Finally, medicinal products for paediatric use are temporarily, totally or partially exempted from cluster rebates under the annual financial regulation.

## **2.7 Italy**

The measures adopted by Italian Medicines Agency (AIFA) to support paediatric research and the appropriate use of medicinal product for children are laid out below.

A Paediatric Working Group, with advisory competences, has been established since 2006 as part of the Agency. This independent committee, made up by thirteen experts, from hospitals and academic and research institutions and eight members from AIFA, is in charge of the coordination and the evaluation of all issues related to paediatric drugs. The main tasks of the Group are: to contribute to the definition and application of the European Regulatory Directives; to support pharmacovigilance activities; to point out clinical trial needs and priorities; to promote information and education initiatives.

AIFA, through its experts, participates in the activities and meetings of the Paediatric Committee within the European Medicines Agency providing objective scientific opinions on any development plan for medicines to be used in children.

The promotion of independent research on drugs represents one of the strategic tasks assigned to the AIFA by legislation. The general aim of the program is to support clinical research on drugs in areas of interest for the National Health Service (NHS) and where commercial support is normally insufficient.

AIFA set up the program on independent research in 2005, and three calls for proposals (2005, 2006, and 2007) have already been launched. The program consisted of three main areas of drug research:

- Area 1. Orphan drugs for the treatment of rare diseases and drugs for non-responders.
- Area 2. Head to head comparison of drugs and therapeutic strategies.
- Area 3. Strategies to improve the appropriateness of drug use and pharmaco-epidemiology studies.

AIFA’s research program has paid special attention to children which are recognised as a patient population normally excluded by clinical studies. In the three calls for proposal five research topics have been entirely dedicated to paediatrics. Overall, more than thirty-five clinical studies including paediatric patients were approved. Of these, twenty-five could be defined as “dedicated studies”, i.e. conducted only in a paediatric setting (children aged 0-17 years) [see table 1]. Moreover, it is also important to highlight that more than 60% of the approved studies involved paediatric patients with a rare disease. Regarding the financial grants, more than twelve out of eighty million Euros were allocated in the last three calls for proposal in order to promote research focussed on paediatrics.

**Table 1. Paediatric studies approved within AIFA’s program for the independent research of drugs (calls 2005-2006-2007)**

Calls	Approved studies	Studies including paediatric patients	Paediatric “dedicated” studies	Paediatric approved studies	studies
	N	N	N	N	% (approved studies)
2005	54	6	6	12	22,2
2006	51	3	9	12	23,5
2007	46	3	10	13	28,3
Total	151	12	25	37	24,5

## **2.8 Latvia**

### **Measures relating to expertise and advice**

State Agency of Medicines of Latvia provides collaboration between Regulatory authorities, industry and healthcare professionals, including Regulatory and Scientific advice, timely, authoritative expertise and conclusions regarding paediatric research subjects.

## **2.9 Lithuania**

### **Financial grants, bursaries, awards and incentives**

The general public measures to support research, including research into medicinal products for paediatric use, have been approved in Lithuania are laid out below.

The Economic Growth operational programme under EU structural assistance for Lithuania in the 2007-13 period; Annex 1 to this programme, “Research and technological development for competitiveness and economic growth”, provides for the following top-priority measures: “Idėja LT”, “Intelektas LT” and “Intelektas LT+”. Subjects conducting research and development of paediatric medicinal products may receive financial support by taking part in tendering processes.

The priorities for Lithuanian research and development in 2007-10, approved by Government Resolution No 166 of 7 February 2007 (Official Gazette 2007, No 21-766).

Persons who conduct research into medicinal products for paediatric use and have submitted projects under the above-mentioned programme or priorities are eligible to bid for financial assistance.

Lithuania has a system under which the cost of medicinal products is reimbursed for outpatients. Medicinal products, including paediatric medicinal products, for which marketing authorisation has been granted are placed on the list of diseases and medicinal products for the treatment thereof in respect of which costs are eligible for reimbursement and the list of medicinal products in respect of which costs are eligible for reimbursement, in accordance with the procedure laid down by the Minister for Health. In the case of medicinal products for children up to 18-years of age that are included on these lists, 100% of the basic price can be reimbursed (reimbursement in respect of medicinal products for adults is provided at a rate of 100%, 90%, 80% or 50% of the basic product price).

### **Other measures**

A working group, which has drawn up a list of measures to support research into, and the development and availability of, medicinal products, was set up pursuant to an order of the Minister for Health in 2007. On the basis of the measures proposed, it is planned in 2008 to:

- amend Lithuanian national legislation governing procedures for clinical trials involving medicinal products, laying down more detailed requirements to be met by research in which children take part;
- make it possible to give priority to the examination of applications for authorisation to market medicinal products for paediatric use in Lithuania and applications for the inclusion of medicinal products for paediatric use in the List of diseases and

medicinal products for the treatment thereof in respect of which costs are eligible for reimbursement and in the List of medicines in respect of which costs are eligible for reimbursement.

## **2.10 Malta**

Malta does not have any incentives in place which are specific to paediatrics.

In the near future, Malta Enterprise within the Ministry of Finance, the Economy and Investment plans to launch a scheme providing fiscal incentives (tax concessions) to projects embarking on R&D in all sectors. These incentives do not cover what is termed as 'Fundamental Research' but will concentrate only on 'Industrial Research' and on 'Experimental Research' as defined in the EU Research and Development Framework Programme.

The Malta Council for Science and Technology within the Ministry for Resources and Rural Affairs has embarked on the development of a Health Research Strategy, for which note is to be taken of the provisions of the European paediatric regulation.

## **2.11 Poland**

The Law of Clinical Trials Act is being prepared. It is focused only on clinical trials, currently these are regulated in thirteen separate legal acts (acts and regulations). It is yet unknown when the legislative process will come to an end. The draft of this Act contains in Division II (Protection of particular groups of clinical trials participants) Section I a specific regulation on persons under age as participants of the trials e.g.:

- additional conditions for clinical trials;
- lack of parental consent;
- consent of under aged participants,
- content of the trial protocol.

## **2.12 Portugal**

### **Financial grants, bursaries, awards and incentives**

Fee reduction for the authorisation of paediatric clinical trials: a proposal is currently under analysis.

### **Measures relating to research infrastructure**

There is a facilitation platform for the promotion of clinical investigation of paediatric medicines, involving all relevant stakeholders.

### **Measures relating to expertise and advice**

A regulatory and scientific advice unit is being established within the national agency that foresees a fee reduction for requests for advice on paediatric medicines.

## **2.13 Romania**

It is a permanent priority of the Romanian Ministry of Public Health to ensure that the population has access to good quality, safe and effective medicines, and that medicines are used as safely as possibly by patients, especially children.

In connection with financing the research and development of medicinal products for paediatric use, the competent authority in the field of scientific research has announced that in 2005-2007 the state did not finance any programmes relating to medicinal products of paediatric use.

As regards the availability of medicines for children, the Romanian Government has adopted special measures relating to the implementation of a scheme for the reimbursement of the cost of medicines for children that is less restrictive than the scheme in place for adults. Under the scheme, those under the age of 18 (together with other categories of beneficiaries) will be entitled to a 100% reimbursement of the reference price of medicines (the lowest price for a particular international non-proprietary name and pharmaceutical form). In addition, the number of medicines covered by the scheme is larger than that for adults (see the additional list – sub-list C3). Similarly, children under the age of one-year receive these medicines for free. The cost of the medicines is paid for out of the Single National Health Insurance Fund. The specific provisions are provided in the Framework Contract relating to the conditions for the granting of medical assistance under the health insurance system for 2007, approved by Government Decision No 1842/2006, published in Official Gazette No 1034 of 27 December 2006, as amended.

#### **2.14 Slovenia**

In accordance with the European paediatric regulation, the following measures will be taken by the Agency for Medicinal Products and Medical Devices of the Republic Slovenia (Agency) to support research, development and availability of medicinal products for paediatric use;

- the Agency will operate a fee reduction policy
- priority review of the applications is foreseen by the Agency

A seminar dealing with scope of the European paediatric regulation was held in Slovenia for paediatricians.

#### **2.15 Spain**

Spain has notified the Commission of two Decisions:

- the Decision of 16 January 2007 of call for grants within the Programme for the promotion of Biomedical Research and Health Sciences, for clinical research of non-commercial purposes, using medicines for human use, to be carried out in 2007, in the context of the National Plan on research, development and innovation. One of the priorities for this call is research in the paediatric population.
- the Decision of 12 March 2008 of the Institute of Health Carlos III, to publish the 2008 Call for grants for the “Strategical Action Programme for Health”, in the context of the National Plan on Research, development and innovation.

#### **2.16 Sweden**

## **Measures relating to infrastructure**

As part of the obligations related to the European paediatric regulation, the Medical Products Agency (MPA) is, in collaboration with the Swedish Paediatric Society, conducting three different nationwide surveys on the off-label use of drugs in the paediatric population, covering in-hospital use, out-patient use and OTC use. The in-hospital survey is based on a complete collection of all in-hospital use of drugs for children, by paediatricians during two days on two different occasions. In another survey, using the nationwide pharmacy prescription registry, all out-patient prescriptions to children during the past year will be collected. In a third study, the OTC sales intended for children will be collected. The organization of these surveys will constitute a framework for future studies regarding similar issues.

## **Measures relating to expertise and advice**

The MPA has, via an agreement with the Karolinska Institute, supplied the paediatric committee with an international expert and professor with the specifically requested expertise in vaccinology. Further, as an alternate in the paediatric committee, the MPA has elected a professor in obstetrics & gynaecology with expertise in adolescent medicine and reproductive health. Further, the MPA provides on a regular basis national scientific and regulatory advice to companies and academic research collaboration groups. Last year approximately two-hundred advice meetings were held at the MPA, some of which regarding paediatric issues, partly or solely.

## **Measures targeting small and medium sized enterprises**

The MPA has a specially assigned office serving small and medium sized enterprises in relation to scientific and regulatory advice, clinical trials and applications. Furthermore, the MPA has two leading experts and professors in the committee on orphan medicinal products, one of whom is chairperson of the committee and represents the committee in the scientific advisory working party. As the vast part of orphan designations regard paediatric indications, this is a major commitment from the MPA for the promotion of the development of drugs for children.

## **2.17 United Kingdom**

### Introduction to the National Institute for Health Research

The National Institute for Health research (NIHR<sup>7</sup>) was established in April 2006 to carry out the vision, mission and goals in the UK Government's strategy, 'Best research for Best Health: A new National Health Research Strategy'. The NIHR is committed to establishing the National Health Service (NHS) as an internationally recognised centre of research excellence through supporting outstanding individuals, working in world-class facilities, conducting leading-edge research focused on the needs of patients and the public.

The NIHR Medicines for Children Research Network (MCRN<sup>8</sup>) was created in December 2006 to improve the co-ordination, speed and quality of randomised controlled

---

<sup>7</sup> [www.nihr.ac.uk](http://www.nihr.ac.uk)

<sup>8</sup> [www.mcrn.org.uk](http://www.mcrn.org.uk)

trials and other well designed studies of medicines for children and adolescents, including those for prevention, diagnosis and treatment.

The Network has extensive knowledge and experience of paediatric research, and supports non-commercial, pharmaceutical/biotech-sponsored and investigator-led partnership studies in over one-hundred NHS sites in England that serve approximately 6 million children.

### Aims of the MCRN

The MCRN aims “to facilitate the conduct of randomised prospective trials and other well-designed studies of medicines for children, including those for prevention, diagnosis and treatment”. And by this, it is the intention of the network to:

- Improve the care of children and their families
- Improve the coordination of research
- Improve the speed of research
- Maintain and enhance the quality of research
- Improve the integration of research
- Widen participation in research

### Vision and Strategy

The MCRN has the central objective of developing and providing medicines that are both safe and effective in the treatment of children. The Network aims to provide leadership and a world-class environment to conduct clinical trials of medicinal products for children throughout the whole range of healthcare, and includes the active involvement of children. The MCRN aims to provide considerable benefit for children through the new knowledge gained by excellent research and the improvements in care, which will follow.

The MCRN’s strategic approach to fulfilling its vision includes the development of a research portfolio that:

- Is relevant to all aspects of the Medicines for Children agenda
- Is ambitious and will make a real difference to the health and lives of children in the UK and beyond
- Will be generated by investigators from a wide range of disciplines
- Will have a major focus on clinical trials but will also include all other study design relevant to the overall objective
- Will be informed by the views and perspective of children and families

### Funding the MCRN

The MCRN is funded by the UK Department of Health and works in partnership with the UK Clinical Research network (UKCRN<sup>9</sup>) to improve the UK’s clinical research environment and maximise the development of safe and effective medicines and formulations for children. It currently receives 4.2 million Euros per year from the

---

<sup>9</sup> [www.ukcrn.org.uk](http://www.ukcrn.org.uk)

Department of Health to fund research networks, plus 1.01 million Euros to fund the MCRN Co-ordinating Centre. In addition, in May 2006 the NIHR Health Technology Assessment Programme announced funding for 8 research projects, see table below, in support of the MCRN. They have a total value of 5.95 million Euros.

**Funding agreed by NIHR health technology Assessment programme in support of the MCRN**

<b>Research Type</b>	<b>Institution</b>	<b>Project Title</b>
Primary	University of York	Cryotherapy versus salicylic acid for the treatment of verrucae: A randomised controlled trial.
Primary	Royal Brompton Hospital	Control of Hyperglycaemia In Paediatric intensive care trial (The CHIP trial)
Methodology	London School of Hygiene & Tropical medicine	Death in the context of a randomised controlled trial: a methodological study of policy and practice in neonatal and paediatric intensive care trials
Methodology	University of Liverpool	Processes in recruitment to randomised controlled trials (RCTs) of medicines for children
Primary	Queen Mary, University of London	Early administration to preterm infants of Bifidobacterium breve strain BBG to prevent infection and necrotising enterocolitis
Primary	University Hospital of North Staffordshire	How should asthma in school-aged children be managed when not controlled with low-dose inhaled corticosteroids (ICS)?
Primary	Children's Hospital for Wales	MAGnesium Nebuliser Trial (MAGNET)
Primary	Bristol Royal Hospital for Children	SLEEPS: Safety profile, Efficacy and Equivalence in Paediatric intensive care Sedation: A Comparison of



		Clonidine and Midazolam
--	--	-------------------------

### **2.18 Countries reporting that no specific national measures have been taken**

Apart from the implementation of the provisions of the European paediatric regulation and the nomination of a Member of the EMEA Paediatric Committee, **Ireland** has reported that to date no national measures to support research into, or the development and availability of medicinal products for paediatric use have been taken.

### **2.19 Countries from which replies are still awaited**

Replies to the Commission's requests for information are still awaited from Denmark, Estonia, Finland, Germany, Greece, Hungary, Luxembourg, Slovak Republic and the Netherlands.

**European Commission Services ENTR F2**

**July 2008**

## Annex 1 – projects funded through the EU Framework Programmes

### 7<sup>th</sup> Framework Programme

<i>RESPECT</i>
Grant agreement no.: 201938
<b>Project full title: Relating Expectations and needs to the Participation and Empowerment of children in Clinical Trials.</b>
<b>Project Type : Co-Ordination and Support Action</b>
<p>There are two objectives for this project: firstly to clarify the expectations and needs of children and their families who have participated or who might participate in clinical trials for new drugs in Europe. Secondly, to identify methods by which the expectations and needs can be translated into empowering and motivating participants in future clinical trials research. This will be achieved in three stages. The partners will be from different areas involving patients, clinicians, regulators, and researchers (industry and academic) on a broad basis in order to cover a broad spectrum of diseases.</p> <p>Stage 1) the project will construct a basis for coordination and harmonization. This will involve a literature search and a preliminary workshop. We will build a website for communication within the project and with a wider audience.</p> <p>Stage 2) we will ground our diverse experience and knowledge through benchmarking good practice case studies, and collecting opinions from patients' organisations in Europe. The results will be presented at an expert harmonization workshop composed of all partners of the project. This workshop will identify the operating procedures needed to encourage empowerment and increase motivation for participation in clinical trials.</p> <p>Stage 3) the results of the project will be presented in a series of European conferences. This will ensure that the impact on clinical practice will be facilitated. This will help to improve translational research, which depends upon the clinical trial process being undertaken with sufficiently large populations to ensure the safety and efficacy of new products.</p> <p>Greater participation in clinical trials research will result in more valid and reliable products available for children as envisaged by the EC 1901/2006 Paediatric Regulation. In addition, it will make European health businesses more competitive and will improve the global health in Europe.</p>

## 6<sup>th</sup> Framework Programme

Project acronym: <i>KidsCancerKinome</i>
Project full title: <i>Selecting and validating drug targets from the human kinome for high risk paediatric cancers</i>
Proposal/Contract no. : <i>FP6-2005-LIFESCIHEALTH-6037390</i>
<b>Project Type : SPECIFIC TARGETED RESEARCH OR INNOVATION PROJECT</b>
<p>Each year 15,000 European children are diagnosed with cancer and 25% die of this disease. Survivors frequently suffer from late side-effects of current treatments regimes. Translational research of childhood tumours to identify molecular targets for novel generation drugs is therefore urgently needed. In addition, novel targeted drugs currently developed for adult tumours have to become available for children. Indeed, the EU will in 2006 launch a Paediatric Medicines Regulation to stimulate drug evaluation in children. Nine European research centers devoted to molecular-biologic and pharmacologic studies of childhood cancers and two SMEs therefore engaged in the KidsCancerKinome project. KidsCancerKinome will make a comprehensive analysis of the human protein kinase family. Protein kinases are already excellent targets for many small inhibitory molecules and antibodies designed for adult tumours. Six aggressive childhood tumours (neuroblastoma, medulloblastoma, rhabdomyosarcoma, osteosarcoma, Ewing tumour, acute lymphocytic leukaemia) will be addressed, which are responsible for 50% of childhood cancer deaths. Viral shRNA libraries will be applied to test the entire human kinase gene family for tumour-driving kinases in cell lines. They will subsequently be analyzed for mutations and functional parameters in large cohorts of tumour samples. siRNA mediated inactivation in larger cell line panels will critically validate suitable kinases as drug targets. Novel kinase inhibitors being developed for adult oncology will be tested for in vitro activity against the tumour-driving kinases. When no inhibitor is available, a novel generation of siRNA based nucleic acid drugs (LNAs) will be applied. Successful compounds will be taken further to in vivo validation in established xenograft models of the six childhood tumour types. KidsCancerKinome will contribute to a better understanding of the unique paediatric tumour biology and to the development of new drugs.</p>

Project acronym: **PROTHETS**

Project full title: **PROGNOSIS AND THERAPEUTIC TARGETS IN THE “EWING” FAMILY OF TUMORS**

Contract no.: LSHC-CT-2004-503036

**Project Type : SPECIFIC TARGETED RESEARCH OR INNOVATION PROJECT**

The project through collaborative studies will define prognostic markers and new therapeutic targets in the Ewing’s sarcoma family of tumours (ESFT) to provide rigorous scientific justifications for the development of clinical trials for this rare disease, which is manifested for the most part in children. The main objective of this project is to evaluate the prognostic relevance of selected markers (EWS/FLI-1, secondary genetic alterations, CD99, IGF-IR, NOVH, erbB-2 and TTF1) and the effectiveness of therapeutic approaches targeting some of these molecules. The prognostic value of these markers will be evaluated in retrospective and prospective series of ESFT patients treated across the participating centres. Through statistical analysis, we will verify which factors have the highest prognostic impact in ESFT patients, in terms of overall survival, disease progression, and chemosensitivity. In order to provide the necessary rationale for the forthcoming application of new therapies, the preclinical effectiveness of new drugs (Herceptin, TRAIL) and strategies targeting molecules (CD99, IGF-IR, EWS/FLI1) found to be critical for ESFT will be evaluated. Another major goal of the project is the construction of ESFT c-DNA microarrays and tissue arrays, which will be used for the analysis of different histological subtypes of ESFT, primary and metastatic tumors and poor and good responders to chemotherapy.

Therefore, the expected results are:

- 1) identification of prognostic factors in ESFT;
- 2) definition of patient selection criteria
- 3) creation of new therapeutic bullets against ESFT;
- 4) identification of new therapies;
- 5) creation of new tools for the diagnosis and screening of high-risk groups.

This will lead to:

- 1) the definition of forthcoming risk-adapted strategies and targeted molecular treatments to be advantageously combined with established therapies;
- 2) improved quality of life and survival for ESFT patients;
- 3) prevention on risk in groups at risk.

Project acronym: E.E.T.-Pipeline

**Project full title: European Embryonal Tumor Pipeline**

Proposal/Contract no.: 037260

Project Type : Specific Targeted Research or Innovation Project

Treatment of embryonal tumors (ET) is a challenge for the pediatric oncologist. Innovative translational research is required to exploit available genomic data and implement state-of-the-art technologies to overcome the deficits of current diagnostic and treatment strategies. We will set up a consortium of leading European institutions and SMEs with extensive clinical and technological expertise to establish a unique pipeline for the **comprehensive development and validation of novel diagnostic tools in addition to efficient preclinical drug development for ET.**

Our holistic approach includes:

- 1) Validation of a **chip-based diagnostic platform** tailored specifically for ET including analysis of genes previously shown by the consortium to be affected in ET
- 2) Generation of ET-specific data on **novel array-based platforms** for the development of **diagnostics** at the microRNA and serum proteomics levels
- 3) Extension of an existing **database** designed to warehouse complete clinical and experimental data for neuroblastoma to include all ET entities
- 4) Implementation of a virtual **ET-Biobank** to improve sharing of patient samples
- 5) Functional characterisation of the most **promising molecular targets** previously identified by the partners as a foundation for entry into a drug development pipeline
- 6) Integration of existing disease-specific **mouse models** to evaluate new treatment modalities *in vivo*
- 7) Initial **evaluation of a screening method an antibody** affecting ET cell invasion
- 8) Application of novel bioinformatic solutions for the **meta-analysis**
- 9) **Dissemination** of the novel tools to researchers and clinical study centers in Europe

Our coordinated effort can achieve the critical mass to facilitate the necessary integration of research capacities for translating ET genome data into significant medical progress. Involvement of clinical study centers will ensure a direct link to the bedside, aimed at improving child health and quality of life.

Project acronym : CHILDHOPE
Project Full Title : <b>Chimaeric T cells for the treatment of paediatric cancers</b>
Proposal/Contract no.: 037381
Project Type : <b>Specific Targeted Research or Innovation Project</b>
<p>Leukaemias are the most common cancers affecting children while malignant lymphomas – including non-Hodgkin lymphomas (NHL) – comes in third position after brain tumours. A significant number of children with leukaemia/lymphomas still fail current therapies. The aim of the CHILDHOPE project is to develop a safe and efficient adoptive immunotherapy for children with advanced or refractory malignancies. CHILDHOPE particularly focuses on three paediatric tumours: acute B-lineage lymphoblastic leukaemia, non-hodgkin B-lineage lymphoma and acute myeloid leukaemia.</p> <p><i>The CHILDHOPE project is a new approach in paediatric cancer treatment since it brings from bench to bedside (and back) an innovative technology as yet never applied in children with advanced or refractory haematopoietic malignancies.</i></p> <p>The CHILDHOPE translational research project will focus on:</p> <ul style="list-style-type: none"> <li>• Improving and testing the efficacy and the safety of anti-leukaemia/lymphoma chimaeric T cells in relevant preclinical models <i>in vitro</i> and <i>in vivo</i> in mice.</li> <li>• Scaling-up this technology to numbers suitable for a clinical application in children with haematopoietic malignancies.</li> <li>• Based on biological material obtained from our preclinical models and from children treated with these genetically engineered T cells, dissecting the interface between the host's tumour and immune cells and use this knowledge to understand the mechanisms of anti-tumour action, validate novel targets and diagnostic tools specific to children affected with leukaemia or lymphomas.</li> </ul> <p>The CHILDHOPE project is built on the excellence of a network of EU-based partners with a broad experience in the field of paediatric haematology and oncology, immunology and cell &amp; gene therapies and integrates the international confederation of parents of children with cancer and an SME specialised in the project management.</p>

Project acronym: <b>EUROBONET</b>
Project full title: <b>European Network to Promote Research into Uncommon Cancers in Adults and Children: Pathology, Biology and Genetics of Bone Tumours</b>
Proposal/Contract no.: LSHC-CT-2006- <b>018814</b>
Project Type : <b>NETWORK OF EXCELLENCE</b>
<p>Primary bone tumours are rare, accounting ~0.2% of the cancer burden. Children and young adolescents are frequently affected. Their aggressiveness has major impact on morbidity and mortality. Though progress has been made in pathological and genetic typing, the aetiology is largely unknown. Though advances in therapeutic approaches increased survival, significant numbers of patients (~40%) still die. Within the EuroBoNeT integration will be achieved by staff exchange and website-based discussion forums to increase and disseminate knowledge of primary bone tumours at the molecular level for development of new tools for patient care and cure and technology. With this integration exchange of material (virtual BioBank), Standard Operating Protocols and the use of technology platforms will enable us to obtain statistical significant datasets, otherwise not achievable due to the rareness and large number of sub entities. A joint programme will contribute in obtaining molecular portraits of tumours, separated in 4 research lines (RL). In each RL the biology of the separate group (RL1: cartilaginous tumours; RL2: osteogenic tumours and related sarcomas; RL3: osteoclastogenesis and Giant cell tumours of bone; and RL4: Ewing family of tumours) will be examined by genome wide expression and genomic aberration studies. More specific hypothesis driven approaches will be investigated by RNA/protein expression and mutation analysis. Knowledge on normal growth and differentiation will be gathered through in vitro studies. This would lead to further understanding and identification of markers for malignant transformation and/or progression, <b>as well as identification of therapeutic targets</b>. Next to research, dissemination of knowledge will be achieved by training courses on bone and soft tissue pathology for all interested. The last is required since patients usually do not present themselves at centres, which necessitates spreading of knowledge.</p>

Project acronym: <b>TEDDY</b>
Project full title: <b>Task Force in Europe for Drug Development for the Young</b>
Proposal/Contract no.: <b>005216</b>
Project Type : <b>Network of Excellence</b>
<p>Knowledge generated by sequencing the human genome will enable more effective strategies to prevent, diagnose and treat human diseases, thus decreasing morbidity and mortality. Together with other age groups, children as well should benefit from this epoch-making breakthrough. The application of advances in genomics, biotechnology and therapeutics can provide children with more effective and safer medicines. However, it will require the development of a new research matrix that integrates scientific domains, assesses the impact of findings and follows policies implementation. Furthermore, any attempt to integrate genetic information into medical practice ought to consider human development and maturation, from the prenatal period through adolescence. The TEDDY project aims at optimising the paediatric use of current drugs and promoting the development of new drugs. To fine-tune paediatric research, it focuses on incorporating pharmacogenetics applications, sharing recommendations for better practice, and implementing dedicated tools. Attention will be paid to variability in response, especially with respect to the role of gender factors and time-dependencies associated with the development from prenatal period to adolescence. An integrated framework will be developed to characterise adverse drug reactions (ADRs) and to optimise dosing regimens, by resorting also to research projects on pharmacogenetics variants. Harmonised databases and recommendations will be created for marketed medicines. Training programmes on ethical, scientific and clinical skills will be set up to build research capacity and to promote social awareness. The proposed network will involve different stakeholders in both drug development sector and paediatric clinical practice. European academics, scientists, healthcare specialists and ethics experts will work together with pharmaceutical companies, regulatory agencies and patients associations to attain common objectives. A strong link with existing European networks running clinical trials in children, such as PENTA and PRINTO, will also be established.</p>