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Paediatric Medicines

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SEVENTH FRAMEWORK PROGRAMME

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Paediatric Medicines

- State of play in FP7
- Lessons learned from 2 calls
- What next?
- Projects funded and in the pipeline
- 4th call and beyond

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Health: area 4.2 results
Off-patent medicines

Call	Response	Support	EU contribution	Success Rate
2nd	15 proposals	6 projects	~ 22 mio	40%
3rd	12 proposals	3 projects	~ 18 mio	25%
Total	27 proposals	9 projects	~ 40 mio	33%

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Lessons learned from two calls :

- limited attention to certain areas (e. g. ophthalmology, gastroenterology, psychiatry)
- lack of clarity between the EMEA Priority List of Molecules and the paediatric (clinical) trial needs
- few involvement of some Member States/SMEs/ other stakeholders
- commitment to seek PUMA lacking

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What we have done to mobilise different stakeholders

- **publications**
- **workshops, also in NMS**
- **EU/US EMEA/FDA co-operation**

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COMMENTARY

EU initiatives for research involving children

Fergal Donnelly

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Abstract Further to recent correspondence in the medical press regarding the UK approach (Editorial in Lancet 367:1933, 2006; Smyth and Edwards in Lancet 368:645–646, 2006) to the Paediatric Medicines Regulation (Regulation (EC) no. 1901/2006, 2006), which has now entered into force, we would like to make reference to a number of research based initiatives of the European Union in this field.

Introduction

In 2005, the EU established TEDDY (Task force in Europe for Drug Development for the Young) [18], a European wide Network of Excellence in paediatric drug development, which aims to expand and promote research on the safe and effective use of medicines for children. It will establish research/process standards in paediatric research activities that are dedicated towards significant therapeutic benefits for children, while, at the same time, avoiding unnecessary studies. Its main achievements to date comprise a published report detailing the number and the characteristics of medicines licensed for use in children by the European Medicines Agency (EMEA) in the 10-year period ending in September 2004 [2]. Also included are the results of a number of Europe-wide surveys aimed at a common definition of "off-label" and "unlicensed" use of medicines in children and on the current ethical and legal frameworks regarding paediatric clinical trials.

The Paediatric Medicines Regulation [8] 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 based on high-quality ethical research. This combines a series of obligations and incentives, comprising the possibility of patent extensions in new Marketing Authorisation Applications (MAAs), along with requirements to provide the results of a paediatric study programme, whether positive or negative, or a waiver in the case of where it is neither safe nor ethical to carry out such studies. A key and new incentive is a new marketing authorisation, to be known as the Paediatric Use Marketing Authorisation (PUMA), aimed at the development of off-patent medicinal products for exclusive use in children with an appropriate formulation. This is because 46% of medicines prescribed to children in hospital are either unlicensed for their age group or, if they are, then this is done off-label [4]. Of the children who actually receive medications in hospital, this figure rises to 87% [4] and, in the context of intensive care, up to 90% of paediatric medicines used are not licensed [3]. The PUMA is a type of intellectual property right (IPR) that will protect the clinical data generated in this research so that it cannot be used to support marketing authorisations of other medicines for a set period of 10 years.

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Funding

The recently adopted Seventh Framework Programme of the European Community for Research, Technological Development and Demonstration Activities (2007–2013) [5] will provide funding for research consortia who wish to engage in this research. This will take the form of clinical and other studies aimed at the generation of pharmacokinetics (in vivo and in vitro) and efficacy and safety data. The development of appropriate paediatric medicinal formulations, which are often severely lacking, is an additional objective [1]. Funded studies should, consequently, lead to an eventual PUMA. A list of research priorities, identified in terms of both clinical conditions, as well as off-label products of therapeutic interest, has been drawn up by the EMEA, of which, account must be taken when submitting project proposals [11].

These projects will take the form of small- or medium-scale focussed research collaborative projects, with a maximum potential EC contribution of €8,000,000 each. They should involve a broad range of stakeholders, industry, the small- and medium-sized enterprise (SME) sector, clinicians, academia, regulatory bodies and, especially, patient organisations. All projects proposals will be subject to the usual rules of participation in the European Commission Framework Programmes [7]. The closing date for the receipt of applications was 18 September 2007. Further Calls for Proposals to ensure complete coverage of the research priorities list, which will be updated periodically, are planned annually.

Discussion

We fully agree with the previously expressed view that children deserve the highest standards of research and ethical protection, and these initiatives are committed to providing this. It is hoped that more research can now be initiated in this neglected area and that the outcomes will have a positive impact on the health and well-being of children, while, at the same time, boosting the innovative capacity of European health-related industries and businesses.

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Current Issues

New Paediatric Research Initiatives in the European Union

a report by
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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 47%,[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 Use 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

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[1] Fergal Donnelly, Personal communication.

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Results from 2nd Call

- **15 Proposals received**
- **8 proposals over all evaluation thresholds**
- **6 retained for funding**

- Good coverage of the ages and some conditions listed.
- Good coverage of malignant diseases, infectious diseases, neonatology
- Limited attention given to ophthalmology, gastroenterology or psychiatry, only one proposal in cardiovascular medicine).
- New Member States significantly under-represented.

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Results from 2nd Call

- **LOULLA & PHILLA**

  Development of oral liquid formulations of Methotrexate and 6-Mercaptopurine for paediatric acute lymphoblastic leukaemia (ALL)

- **TINN**

  Aims to evaluate PK & PD of ciprofloxacin and fluconazole in neonates

- **O3K**

  Oral liquid formulations of Cyclophosphamide and Temozolomide

- **NEUROSIS**

  Eefficacy of Budesonide (BS) in reducing bronchopulmonary dysplasia (BPD).

- **EPOC**

  Aims to evaluate pharmacokinetics and pharmacodynamics of doxorubicin

- **NeoOpioid**

  Compares morphine and fentanyl in pain relief in pre-term infants

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Results from 3rd Call

- 12 proposals received

Total budget available	**€ 25 000 000**
Maximum EU contribution*	**€ 6 000 000**

- Wider coverage of topics
- Psychiatry, Infectious diseases, Immunology
- Higher scores if participating US centres

**per project*

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Results from 3rd Call

- **NEMO**

  Evaluates the efficacy safety, PK, PD, mechanisms of action of bumetanide in neonatal seizures, including the effect on neurodevelopment and to develop and adapt a bumetanide formulation suitable for newborns in order to apply for a Paediatric Use Marketing Authorization (PUMA).

- **NeoMero**

  European multicentre network to evaluate pharmacokinetics, safety and efficacy of Meropenem in neonatal sepsis and meningitis

- **PERS**

  Focuses on two indications, the use of risperidone in children and adolescents with conduct disorder who are not mentally retarded, and the use of risperidone in adolescents with schizophrenia

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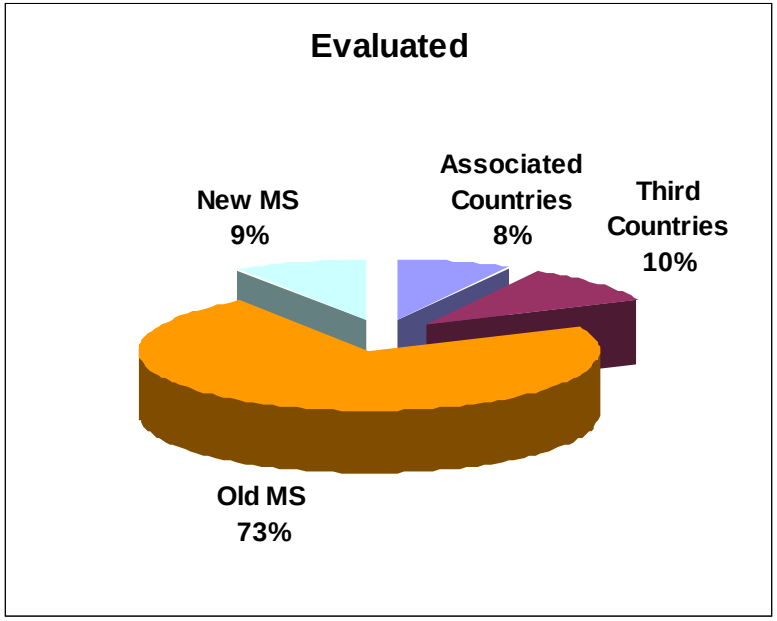
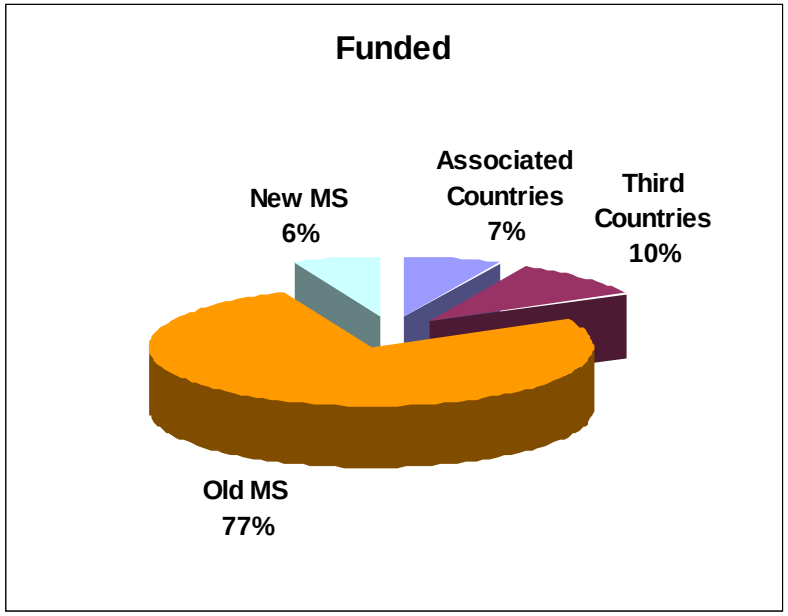
Results from 2nd Call





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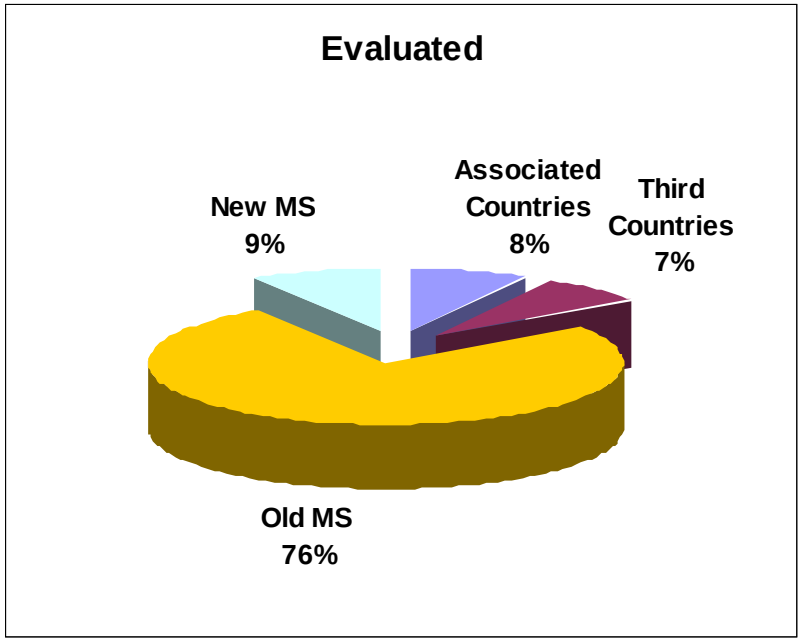
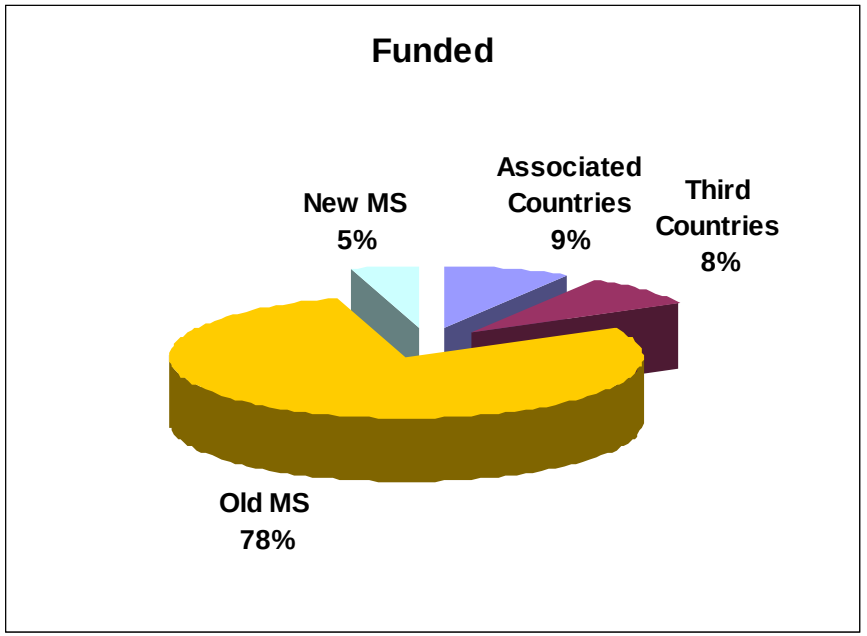
Results from 3rd Call





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What to do next?

- SME workshops : EMEA, 23 October 2009
- Paediatric societies, other organisations
- EU/US/Third Country co-operation
- Joint activities with DG ENTR
- Specific publications: flyers etc

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SMEs : Commission Regulation (EC) No 2049/2005

- Administrative and procedural assistance from the SME Office at EMEA;
- Fee reductions for scientific advice, inspections and (for veterinary medicines) establishment of maximum residue limits;
- Fee exemptions for certain administrative services of the EMEA;
- Deferral of the fee payable for an application for marketing authorisation or related inspection;
- Conditional fee exemption where scientific advice is followed and a marketing authorisation application is not successful;
- Assistance with translations of the product information documents submitted in the application for marketing authorisation.

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SMEs

To determine which companies are eligible for SME incentives, the EMEA will apply the definition of micro, small and medium-sized enterprises provided in *Commission Recommendation 2003/361/EC*

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4th Call for Proposals area 4.2

- **Opened 30 July 2009, deadline 19 November 2009**
- **Specific topics for OPM (in collaboration with EMEA - PDCO) :**
  - new formulations, for example oral presentations for existing products (oncology, pain relief, etc.),
  - the needs of neonates (in infectious diseases, neurology, analgesia, intensive care),
  - age-appropriate formulations and
  - new conditions (rheumatology, etc).

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4th Call for Proposals area 4.2

- **Greater EU-US Co-operation :**
  - EU-US science & biotechnology agreement
  - EU-US Transatlantic Co-Operation Council
  - Paediatric Medicines Regulation, BPCA, PREA
- **International Paediatrics Initiative**
  - Closer integration of EU research in paediatrics
  - Closer integration with research in paediatrics in US, Third Countries
  - Jointly executed research activities in support of these goals
  - Spreading of excellence – training : joint Paediatric Clinical Pharmacology training programme

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4th Call for Proposals area 4.2

Paediatric Clinical Pharmacology Training Programme – main elements

- **Ethical Issues of Clinical Trials in Children**
- **PK, PD studies in Children**
- **Drug action and effect in paediatric patients**
  - Age to age efficacy extrapolation
  - Efficacy/safety predicitivity in small populations
  - Validation of end-points, biomarkers
- **Drug toxicity in children**
  - Non-clinical signals
  - Pharmacovigilance
- **Socio-political and regualtory aspects of medicines in children**
  - EU, US, Japan differences, EU-US dialogue, ICH
- **Pharmacoeconomics**

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  http://cordis.europa.eu/fp7/dc/index.cfm?fuseaction=UserSite.CooperationCallsPage&id_activity=1

- **Work Programme, incl. Paediatric Medicines :**

  http://cordis.europa.eu/fp7/dc/index.cfm?fuseaction=UserSite.CooperationDetailsCallPage&call_id=10

- **Independent Expert registration**

  https://cordis.europa.eu/emmfp7/index.cfm?fuseaction=wel.welcome

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