ICORD

Teddy Network of Excellence

Funded under the Community's Sixth Framework Programme

Global Approaches for Rare Diseases and Orphan Products

5th International Conference on Rare Diseases and Orphan Drugs

Linking Academic Discoveries and Industry Product Development Strategies

TEDDY contribution

TEDDY

Task-force in Europe for Drug Development for the Young

ADRIANA CECI, TEDDY NoE Coordinator

24 February 2009

TEDDY is a **Network of Excellence** funded under the 6° Framework Program, encompassing 19 Research Centers and 10 European Countries and Israel and is cooperating with more than 200 researchers and experts

Aimed at increasing availability of paediatric safe and efficacious drugs

WHICH TEDDY MISSION?

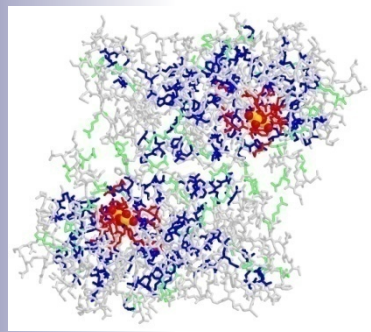
In compliance with the Second Call of the FP6 (2003): LSH-2003-1.2.1.1 Medicines for children - NETWORK OF EXCELLENCE TEDDY should operate in order to

structuring efforts devoted to the development of medicines for children by

- covering all aspects involved
- giving particular emphasis on the design of medicines for **small populations**
- developing close **collaboration among academia, pharmaceutical industry**, ethical bodies and regulatory authorities

ACTIVITIES AND PRINCIPAL RESULTS

Surveys, data collection and bibliographic searches have been used to picture the current situation as well as to identify research priorities



Common expertises, material and human resources have been exchanged and shared to plan Paediatric innovative research and methodologies

Disseminate and provide opinion on key documents and institutional rules and guidelines with reference to paediatric needs, methodological aspects, ethic, comunication, etc

Paediatric Medicines in Europe

The aim of this presentation is to discuss:

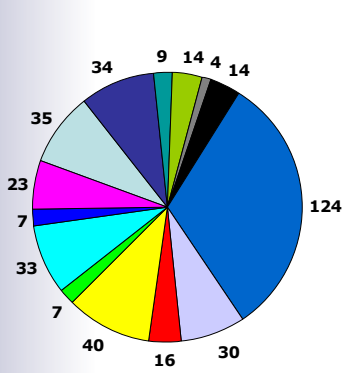
the role and the experience of TEDDY in the Paediatric Medicines Development approach on the light of the Paediatric Regulation

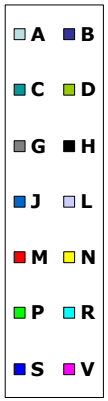
the advantages possibly deriving to the 'orphan drugs' sector from the approval of the Paediatric Regulation

TEDDY – European Paediatric Medicines Database
Medicines approved to be used in the paediatric population

Ceci A. et al, Eur J Clin Pharmac, July 2006

DECENTRALISED N=443/1200

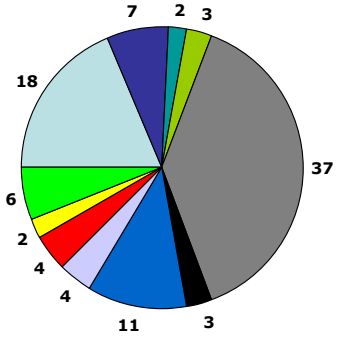


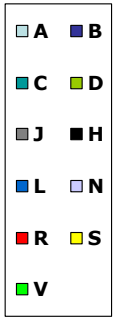


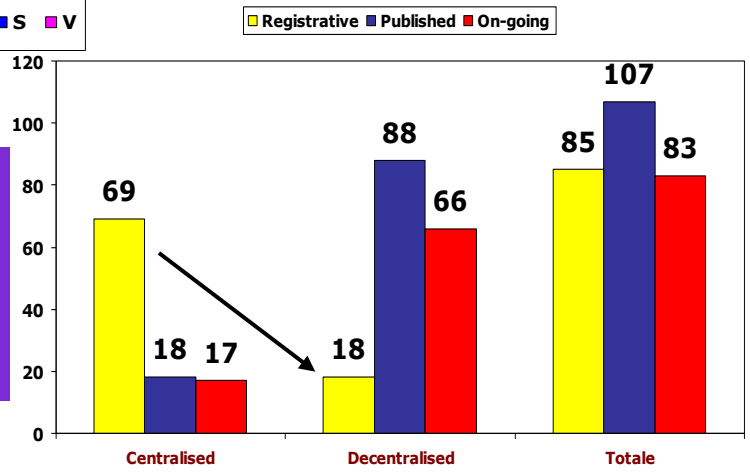
n. Orphan	23
n. Paediatric	11
With Paed. St.	34%

Existing Studies

CENTRALISED N=97/302



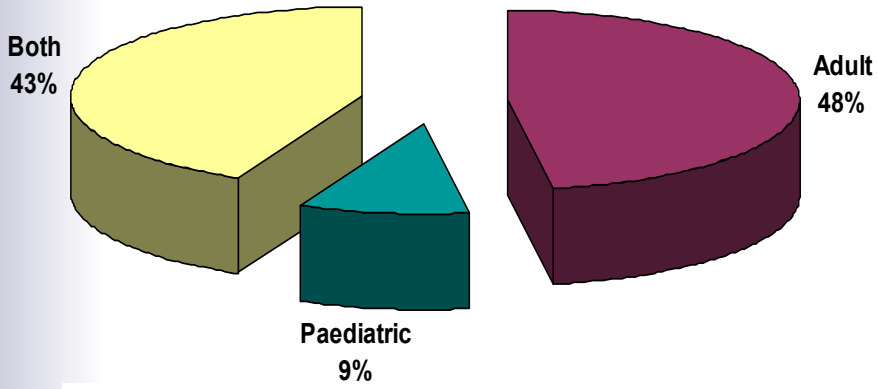


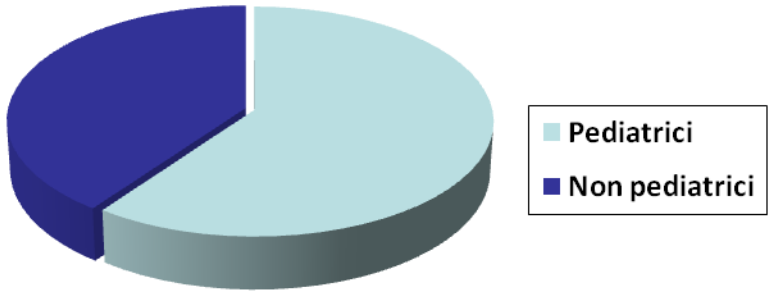


Less than 50% of Paediatric Medicines have been studied in children

Registrative studies are increasing in the Centralised versus Decentralised procedure

Orphan Drugs and Paediatric Population COMP-Statistics





51% of Orphan Drugs are designated for paediatric conditions

Only 40% of orphan drugs needed in children are approved for them

CHILDREN ARE ORPHAN TWO TIMES!!

Linking Paediatric and Orphan Drugs:
Paediatric & Orphan Drugs: same fate

Rare diseases often affect children because:

- Are Genetic Diseases
- Are caused by an inborn metabolic error
- Start early in the life
- Affect growth, sexual and CNS maturation during the developmental process

Few specific information are available because:

- The small number of patients affected by each condition.
- The small amount of resources invested to increase specific knowledge.

The use of medicines not specifically tested for the condition (off-label, unlicensed, experimental).

Clinical trials more difficult, take longer and cost more

Paediatric & Orphan Drugs: same fate USA experience

- Pediatric population, growth and developmental changes can influence the way drugs are absorbed, distributed, metabolized, and excreted, which are vastly differently from the adult
- Paediatric patients constitute a "medically plausible" subset of patient population.

In USA a pediatric indication is considered a new "orphan" indication,

Sponsor may request orphan-drug designation.

FDA U.S. Food and Drug Administration

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 12 December 2006

What in Europe???

The **Paediatric Regulation** lays down rules concerning the development of medicinal products for human use, in order to meet the paediatric population needs

OBLIGATION:

Paediatric Investigation Plan (PIP)

(or **waiver** or **deferral**)

before a MA application for:

- new indications
- new route of administration
- new pharmaceutical form

VOLUNTARY

Non-patented drugs could access a PUMA (Paediatric Use Marketing Authorisation)

REWARDS

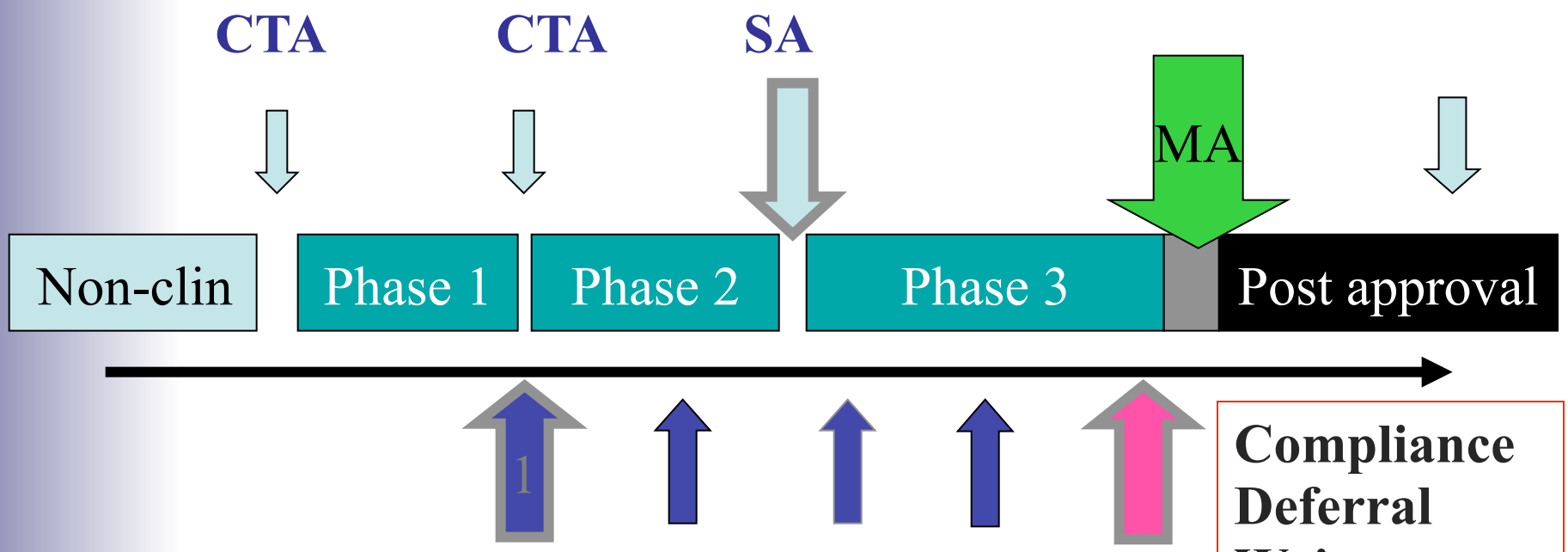
Patent or Supplementary Protection Certificate: extension of 6 months

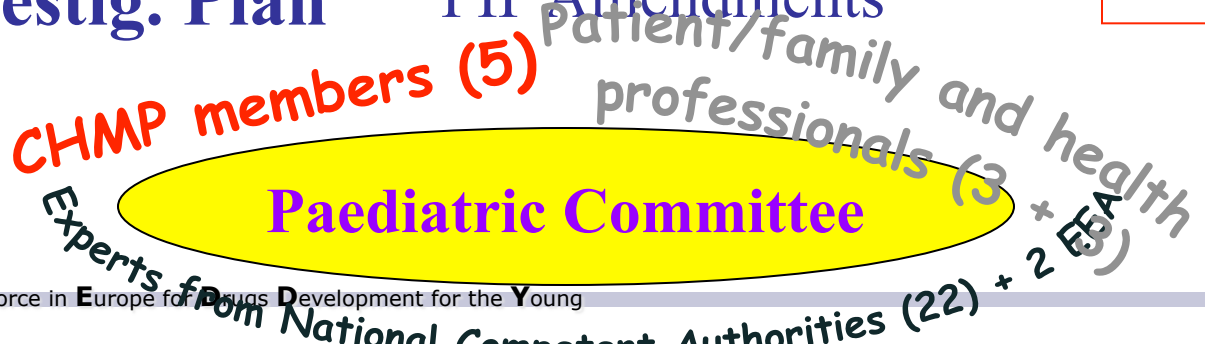
In case of Orphan Drugs a 12 instead of 10 years of market Exclusivity

Funds from the EC (and Member States) for Non-patented drugs in the 'Priority List'

Paediatric Regulation

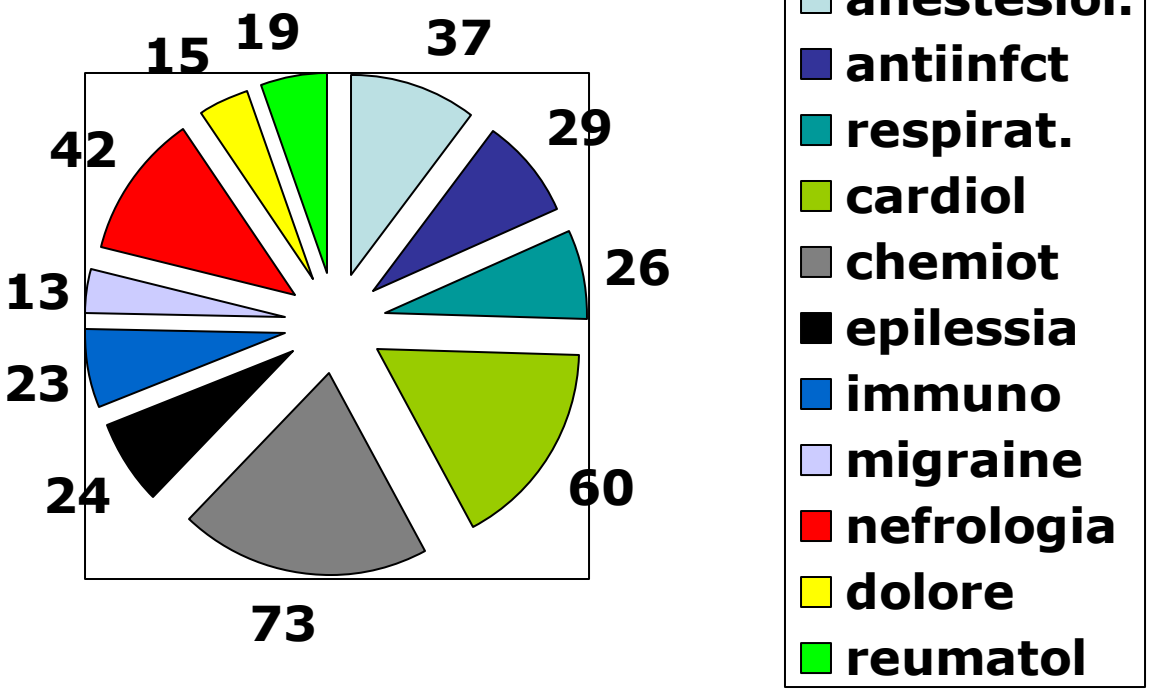
A new Procedure (PIP)
A new Committee: PDCO





PDCO PRELIMINARY ACTIVITIES
PIPs Application

293 requested – approved 74



Therapeutic Needs- Lists

	Reference	Notes
Anaesthesiology		
Assessment of the paediatric needs - Anaesthesiology	EMEA/405166/2006	
Anti-infectious therapy		
Assessment of the paediatric needs - Anti-infectious therapy with focus on antimycotics, antivirals (except HIV)	EMEA/435350/06	
Cardiology		
Assessment of the paediatric needs - Cardiovascular products	EMEA/436949/06	See also the comments received during consultation on this list: EMEA/404310/06
Chemotherapy I (Cytotoxic therapies)		
Assessment of the paediatric needs - Chemotherapy products (Part I)	EMEA/CHMP/384641/06	See also the comments received during consultation on this list: EMEA/CHMP/384188/06
Chemotherapy II (Supportive therapy)		
Assessment of the paediatric needs - Chemotherapy Products (Part II)	EMEA/CHMP/224696/06	
Diabetes (Types I and II)		
Assessment of the paediatric needs - Diabetes (Types I and II)	EMEA/224688/06	
Epilepsy		
Assessment of the paediatric needs - Epilepsy	EMEA/CHMP/377147/06	See also the comments received during consultation on this list: EMEA/CHMP/377231/06
Gastroenterology		
Assessment of the paediatric needs - Gastroenterology	EMEA/527934/07	
Immunology		
Assessment of the paediatric needs - Immunology	EMEA/CHMP/381922/06	See also the comments received during consultation on this list: EMEA/CHMP/381452/06
Migraine		
Assessment of the paediatric needs - Migraine	EMEA/224515/06	

Lists of **therapeutic needs** have been prepared from a Public Health perspective.

The starting points have been

- current and potential use,
- legal status
- available paediatric information
- appropriate formulations

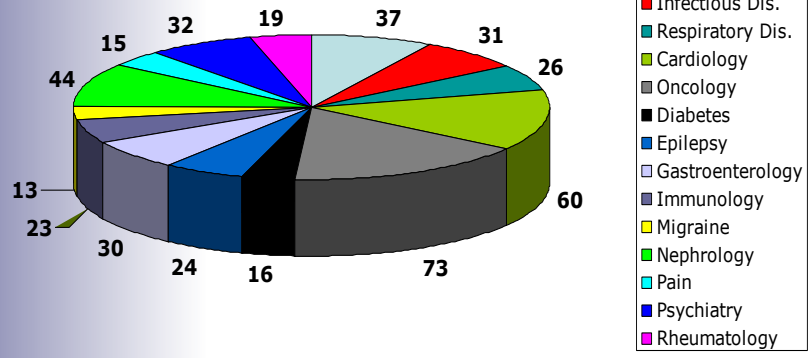
Nephrology		
Assessment of the paediatric needs - Nephrology	EMEA/13306/07	
Obstructive lung disease		
Assessment of the paediatric needs - Asthma and other obstructive chronic lung diseases	EMEA/439727/06	
Pain		
Assessment of the paediatric needs - Pain	EMEA/CHMP/18922/05	
Psychiatry		
Assessment of the paediatric needs - Psychiatry	EMEA/288917/07	
Rheumatology		
Assessment of the paediatric needs - Rheumatology	EMEA/CHMP/234105/2005	See also the comments received during consultation on this list: EMEA/207562/06

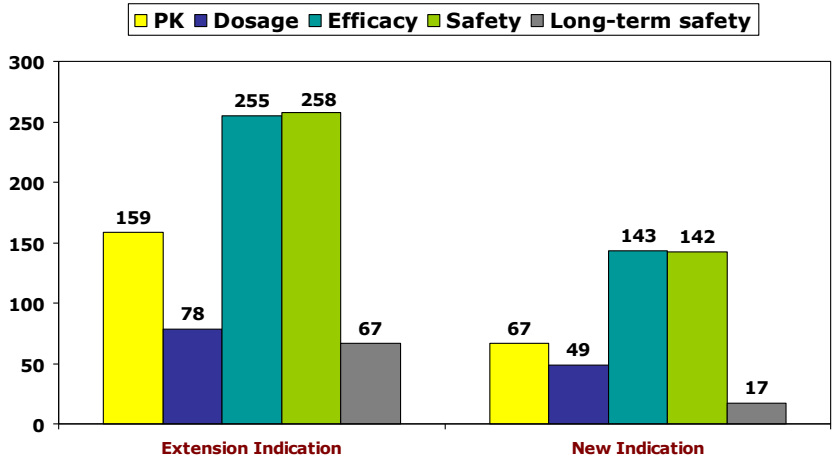
Paediatric Regulation expected impact

Drugs and Requested studies: analysis from the EMEA lists

14 Therapeutic areas:
443 drugs of interest for children

Many clinical studies are requested:
clinical, non-clinical,
formulation long-term safety, ecc.



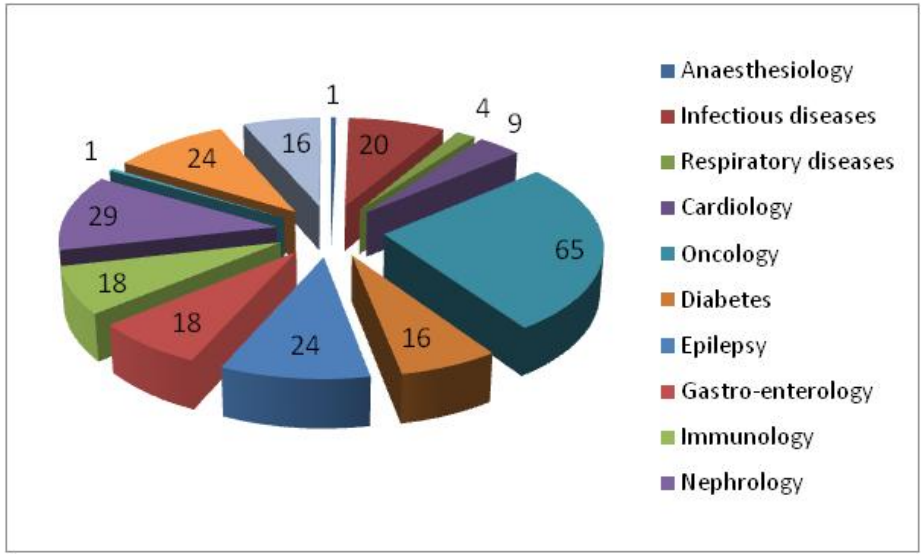


PDCO requests: Costs and advantages

According to the RAND 2006 study:

- in 2015 there will be over 150 million children in the EU
- the costs of developing **the paediatric investigation plan** will increase the costs to industry of 1-7 (average 4) million Euros per product.
- **The cost of Phase III clinical trials will increase of 25% in the first year and between 7% and 16% in the following years**
- The increase in costs would then translate into a price rise of 0.1% to 0.4%.

10 Therapeutic areas
245 medicines
to be developed for children
for **treatment of rare diseases**



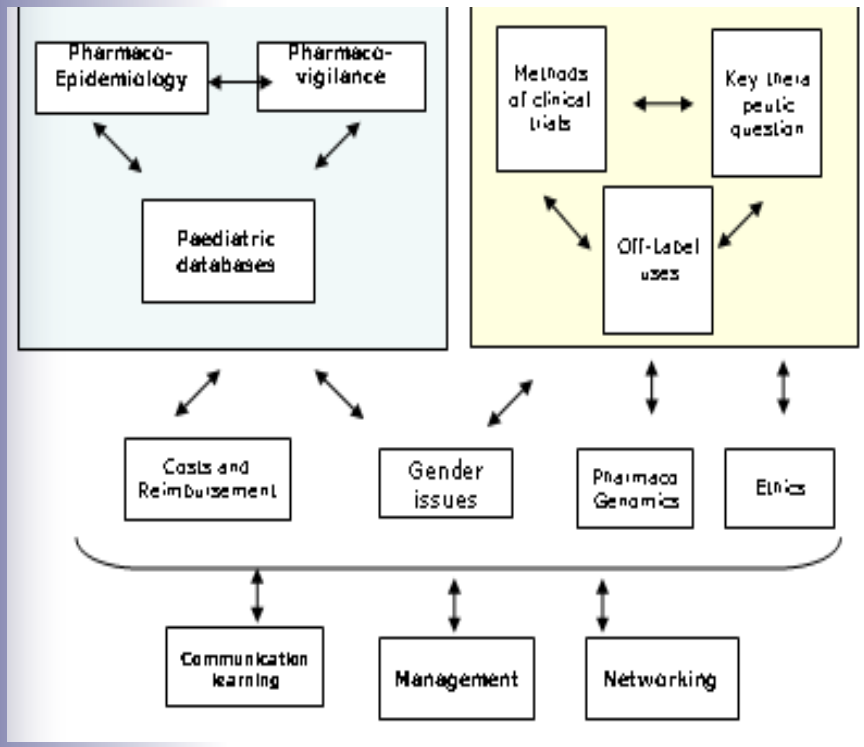
TEDDY, Pharmaceuticals Policy and Law, 2009 (in press)

Paediatric Regulation impact on scientific community, industries and regulators

AREA	Main Paediatric Needs/ TEDDY expertises
• **Preclinical**	• Juvenile animals studies • Non-clinical signals • PK/PD modelling • Age to age efficacy extrapolation • Safety studies in the appropriate subsets • Studies on formulation prototypes • Efficacy/safety predictivity in small populations • Validate end-points (scale, non-invasive, etc) • Paediatric data integration and management (biological, pharmacoeidemiological, clinical trials, Adverse Events and Reactions)
• **Toxicology and Safety Evaluation**	
• **Efficacy Evaluation**	
• **Long-term safety**	
• **Education and Training**	

TEDDY NoE experiences in the light of the Paed. Reg.

TEDDY NoE STRUCTURE



Networking has been one of the more relevant activities of TEDDY and has also facilitated the achievement of its main project results as surveys, data banking, innovative methodologies identifications, inventories of researchers and research, and so on.

Scientific Results

11 PR publications, 1 Monograph 3 Methodological testbooks, 1 Website , 3-monthly news-letters

Succesful Networking activities
Collaborating Poeple

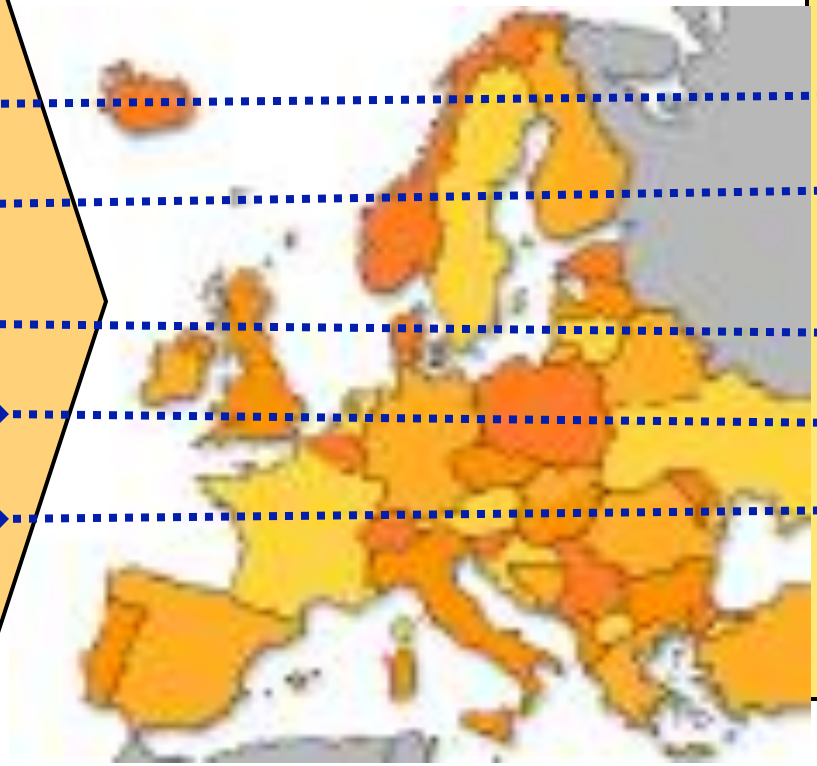
Academy & Researcher •410

Public Health •210

Other Professional •48

Industries • 94

Associations •30



European Countries: 25

No European Countries: 8

The Network of Paediatric Networks at the EMEA Implementing Strategy

European Medicines Agency

London, 15 January 2008
Doc. Ref. EMEA/MB/543523/2007

The Network of Paediatric Networks at the EMEA Implementing Strategy

4. Existing paediatric networks

In parallel to the meetings held at the EMEA in 2005 and 2006, an informal inventory has identified that many different paediatric networks, investigators and centres with specific expertise*[1] exist in the Community, or are under construction. The relevant networks are those with an interest in the development of medicinal products. They can be identified as:

- national networks, generally benefiting from public funding (at present 7 national networks have been identified),
- European networks publicly funded, such as TEDDY (Task Force in Europe for Drug Development of the Young) which is funded through the 6th Framework Programme,
- paediatric 'sub-speciality' networks at European level and beyond, which group centres working in the same therapeutic area (e.g. HIV infection, rheumatology),
- age-related networks (e.g. neonatal networks),
- activity or structure-related networks (e.g. community-practitioners networks, hospital-based dedicated clinical-research centres linked by a common structure, pharmacovigilance networks)
- networks including paediatric centres but not dedicated solely to paediatric research.

The inventory will be expanded and developed.

Succesful Networking activities

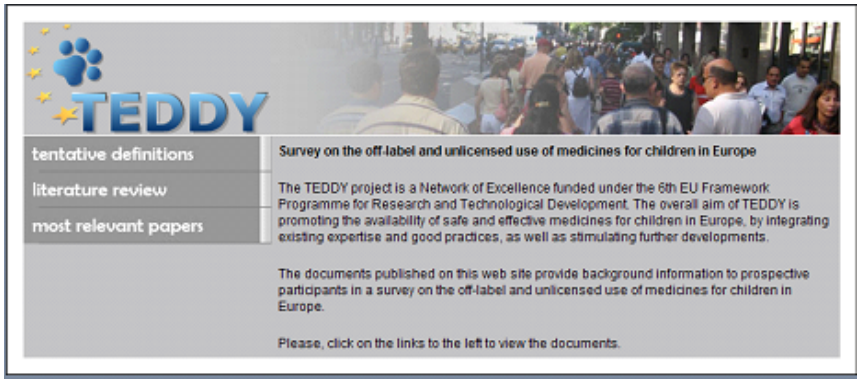
Defining off-label and unlicensed use of medicines for children: results of a Delphi survey.

The aim of this Delphi survey is to develop common definitions for unlicensed and off-label drug use in children to be used for research and regulatory purposes. After a literature review on the current status of unlicensed/off-label definitions, a two-stage, web-based Delphi survey was conducted among experts in Europe. Results were then consulted with the European Medicines Agency (EMEA)

The lowest level of consensus reached was for questions related to a different formulation or if a drug was given although contraindicated. At the final step, 85% of the responding experts agreed on the proposed definition for off-label (use of a drug already covered by a Marketing Authorisation, in an unapproved way) and 80% on the definition for unlicensed.

Table 1: Composition of the Expert Panel

	Invited % (n)	participants % (n)
Health Professionals	14.29 (12)	20.59 (7)
Industry	8.33 (7)	8.82 (3)
Regulatory	20.24 (17)	14.71 (5)
Scientists	52.38 (44)	55.88 (19)
Other	4	0
Total	84	34



Pharmacol Res. 2008 Nov-Dec;58(5-6):316-22. Epub 2008 Sep 18

Succesful Networking activities

European Surevy on ethical and legal framework, Journal International de Bioéthique, sept. 2008, vol.19, n.3, pp.17-48.

A survey investigating the ethical and legal context in European Countries has demonstrated a jeopardised situation regarding consent, assent, general awareness on ethic rules to be applied.

Question on:

1. Selection criteria (only direct benefit?)
2. Authorization/assent procedure (relevance of the minor opinion)
3. Information and privacy (any information according to the minor's capacity)
4. Emergency situation

27 European Countries participated the Survey

770 Questionaires to be further circulated

Res/Paed	202
Pharma I.	167
Other	33

Teddy Network of Excellence
Funded under the Community's Sixth Framework Programme

EUROPEAN SYMPOSIUM
Ethics and paediatric clinical research in Europe

Succesful Networking activities

Collecting pediatric data in the EU for pharmacoepidemiology and pharmacovigilance

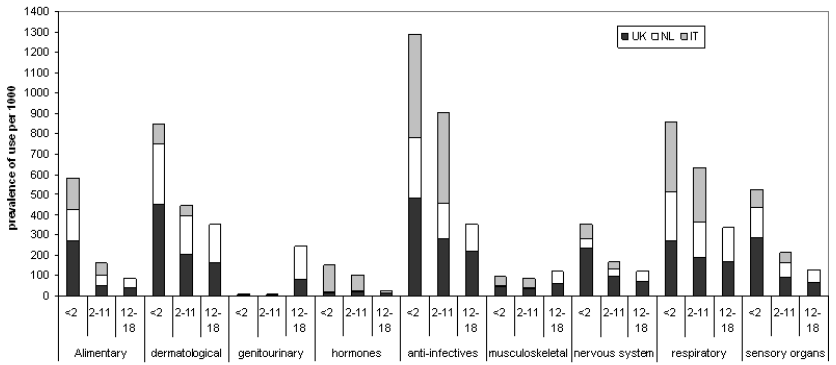
Assessment of 16 databases from 10 EU Countries

8 million children

		Cohort, Case-Control Studies	*Drug utilisation studies*	IMS DA UK	Pedianet	IPCI	GPRD	THIN Data	QRESEARCH	SPICE	IMS DA FRANCE	IMS DA AUSTRIA	IMS DA GERMANY	PHARMO	IADB	The Danish Prescription Database (NPD)	Finland prescription register	PEM	Swedish Medical Birth Register
	Unique Identifier	yes	no																
	Age	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	Gender	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	Death	yes	no	yes	yes	yes	yes	yes	yes	yes	no	no	no	yes	yes	no	no	yes	limited
Prescriptions (Drug exposure)	Prescriptions	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	Unique product code	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	ATC Code	yes	yes	yes	yes	no	no	yes	yes	yes	yes	yes	yes	yes	yes	?	yes	yes	yes
	Date of prescription	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	no
	Dosage of prescription	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	yes
	Duration of prescription	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes	yes
Outcomes	Laboratory values	yes	no	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	no	no	no	yes	no
	Diagnostic data (e.g. x-ray, MRT, etc.)	yes	no	yes	yes	yes	yes	yes	limited	no	no	yes	yes	yes	no	no	no	yes	no
	Treatment outcome	yes	no	yes	yes	yes	yes	yes	yes	no	no	no	no	yes	no	no	no	yes	no
	Hospital admission	yes	no	yes	yes	yes	yes	yes	limited	no	no	yes	yes	yes	no	no	no	yes	no
	Hospital discharge diagnosis	yes	no	no	yes	yes	yes	yes	limited	no	no	no	no	yes	no	no	no	yes	no
	Referral to specialist	yes	no	yes	yes	yes	yes	yes	limited	no	no	yes	yes	yes	no	no	no	yes	no
	Results of referral visits	yes	no	yes	yes	yes	yes	no	limited	no	no	no	no	yes	no	no	no	yes	no
Confounders	Diagnosis	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	no	no	yes	yes
	Medical history (anamnesis)	yes	no	yes	yes	yes	yes	yes	yes	yes	no	no	no	yes	no	no	no	no	no
	Vaccination	yes	no	yes	yes	yes	yes	yes	yes	yes	no	no	no	yes	no	yes	no		no
	Allergies	yes	no	yes	no	yes	yes	yes	yes	yes	no	no	no	yes	no	no	no	limited	no
	Indication for prescription	yes	no	yes	no	yes	yes	limited	limited	no	yes	yes	yes	no	no	no	limited	yes	no
	Height	yes	no	yes	yes	yes	yes	yes	yes	no	no	no	no	yes	no	no	no	no	yes
	Weight	yes	no	yes	yes	yes	yes	yes	yes	no	no	no	no	yes	no	no	no	no	yes
	Environmental and life-style characteristics	yes	no	yes	yes	yes	yes	no	no	no	no	yes	yes	yes	no	no	no	no	no
Data access	Access to raw data	yes	no	yes	no	yes	yes	yes	yes	no	yes	yes	yes	yes	no	no	yes	no	yes
	Access to original medical charts	yes	no	no	yes	yes	yes	no	no	no	no	no	no	yes	no	yes	no	no	no

Databases for pediatric medicine research in Europe--assessment and critical appraisal. Pharmacoepidemiol Drug Saf. 2008 Dec;17(12):1155-67.

Drug use in children: cohort study in three European countries. BMJ. 2008 Nov 24;337:a2245. doi: 10.1136/bmj.a2245.



Asthma drug use in children in the Netherlands, Italy and United Kingdom
(E. Fatma. Sen, et al submitted)

The Prescribing of analgesics and Non-Steroidal Anti-Inflammatory Drugs in Paediatric Primary Care in the UK, Italy and the Netherlands (Antje Neubert[1], et all)

TEDDY Task-force in Europe for Drugs Development for the Young

PAEDIATRIC STATUS AND OFF-LABEL USE OF DRUGS IN CHILDREN

(ITALY, UNITED KINGDOM AND THE NETHERLANDS)

- **One hundred-forty three** active substances corresponding to 269,590 prescriptions evaluated (the most prescribed)
- **25%** show the same Lowest Approved Age in all three countries
- **8 of the drugs** in almost two databases have a similar approved minimum age
- **2 of the drugs** in all databases have a similar approved minimum age
- The **off-label use by age** is maximum in The Nehederland

	United Kingdom		Italy		The Netherlands	
	N. of drugs	%	N. of drugs	%.	N. of drugs	%
0 – 2 years	26	40.0	33	47.1	25	40.3
2 – 11 years	27	41.5	25	35.7	18	29.0
12 – 17 years	7	10.8	2	2.9	2	3.2
> 18 years	5	7.7	10	14.3	17	27.4
Total	65	100	70	100	62	100

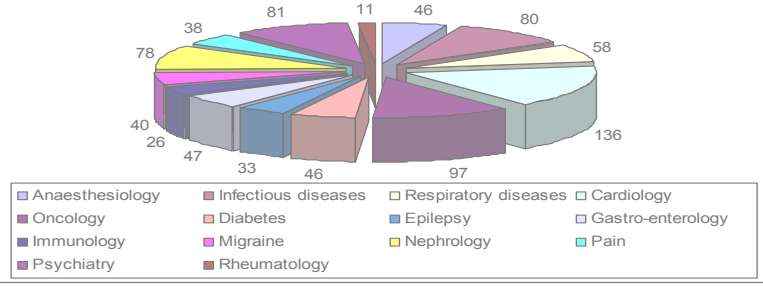
Succesful Networking activities

Networking & Unmet Therapeutic Needs

PK/Dosage/Efficacy & Safety (extension to paediatric ages)		PK/Dosage/ Efficacy & Safety (new indic.)	Age appropriate formulations	
Adenosine TP	Iloprost	Atorvastatin	Metoprolol	Low Molecular Weight Heparins
Alteplase	Inhaled Nitric Oxide	Colesevelam	Acebutolol	Warfarin
Amiodarone	Irbesartan	Fluvastatin	Esmolol	Indometacin
Amlodipine	Labetalol	Hydrochlorothiaz / Chloroth	Amiodarone	Clonidine
Arginine-Vasopressin	Levosimendan	Lovastatin	Flecainide	Labetalol
Atenolol	Lidocaine, as anthiarrhytmic	Pravastatin	Adenosine Tp	Milrinone
Atorvastatin	Lovastatin	Simvastatin	Lidocaine	Sildefanil
Bosentan	Low Molecular Heparin		Furosemide	Iloprost
Candesartan	Metoprolol		Spironolattone	Dopamine
Captopril	Milrinone		Hydrochlorothiaz / Chloroth	Dobutamine
Carvedilol	Nicardipine		Irbesartan	Arginine-Vasopressin
Clonidine	Nifedipine		Candesartan	Di/Hydralazine
Clopidogrel	Nitroprusside		Valsartan	Nitroprussiate Na
Colesevelam	Pravastatin		Atorvastatin	Captopril
Dalteparine	Prazosin		Fluvastatin	Ramipril
Di/hydralazine	Propafenone		Urokinase	Niferipine
Dipyridamole	Propranolol		Clopidogrel	Verapamil
Dopamine	Ramipril		Alteplase	Amlodipine
Enalapril	Sildenafil		Enoxaparine	Nicardipine
Enoxaparine	Simvastatin		Dalteparine	Prazosin
Enoximone	Sotalol		Acetylsalicylic Acid (Aspirin)	Propranolol
Esmolol	Telmisartan		Heparin	Sotalol
Flecainide	Urokinase			Carvedilol
Fluvastatin	Valsartan			Atenolol
Furosemide	Verapamil			
Hydrochlorothiaz / Chloroth	Warfarin			

150 Experts in Europe

13 Therapeutic areas - 478 drugs



Succesful Networking activities

Networking & Unmet Therapeutic Needs

Health-care Development

Challenges in prescribing drugs for children with cancer

Paediatric oncology has achieved high cure rates despite the limited availability of drugs that have been specifically studied for use in children with cancer. Efficacy of these drugs has received more attention than their safety, but permanent side-effects in growing children need to be considered. An absence of pharmacokinetic data, dose-defining studies, schedules defined by age, and appropriate formulations can lead to underdosing or overdosing in specific age groups, resulting in a potential lack of benefit, development of resistance, and increased adverse drug reactions. These major clinical concerns have promoted initiatives in Europe since 2003 regarding the need for a Paediatric Regulation, aimed at improving the risk–benefit ratio of such drugs in children and providing the legal framework to overcome the limitations of the past. However, to undertake the appropriate studies of these drugs in this setting, financial support is essential. Europe is now showing its commitment to overcome the present difficulties of drug prescribing for children with cancer by introducing measures that will encourage new public–private partnerships. All those involved, including researchers, paediatric oncologists, learned societies, regulatory agencies, national agencies, and pharmaceutical companies, need to become more familiar with the opportunities opened up by the new regulation, which is aimed at providing an increased cooperation between researchers and drug developers for the benefit of children.

Introduction

Successful use of chemotherapy in children with cancer started in the 1960s with drugs such as vincristine, mercaptopurine, and methotrexate. Paediatric oncologists continued to use the armamentarium of drugs developed for adult cancers and, nowadays, about 75% of newly diagnosed children with cancer are expected to be cured (figure 1).[1] This success story has been achieved through collaborative, mainly non-commercial, clinical trials and improvements in supportive care. However, few formal studies have taken place on the pharmacology of these drugs in children, and even fewer trials sponsored by drug companies have aimed to show the antitumour efficacy of these drugs against cancers specific to childhood in order to support a licensed indication. Currently, in both Europe and the USA, an estimated 80% or more of drugs used to treat children with cancer do not have information for paediatric use in their product licence and are, thus, used off-label.[2,3] However, less than 19% of drugs approved for adults with cancer and less than 50% of those commonly used have a role in paediatric oncology.

When using such drugs in children, potential acute and chronic effects should take into account changes during the developmental stages from infancy to adulthood. Physiological and psychological changes might also occur due to the effect of treatments that inhibit the growth of tissues and organs (eg, radiation and certain drugs).[4] Therefore, a new EU Paediatric Regulation has been formed to fulfil equal treatment opportunities for children as for adults and to substantiate an ethical change in the balance between risk and benefit for assessing the use of drugs in children.[3,4] However, the barriers to undertaking proper research on children's drugs are long standing and include: the cost of studies compared with the size of the potential market; difficulties in trial design (eg, small numbers of eligible patients and lack of appropriate age-matched controls); long approval processes and increases in the time taken to complete studies in children compared with in adults; and the unique and complex ethical issues surrounding research on children and assessment of risk–benefit in those who cannot provide consent for themselves. Paediatric clinical trials of new drugs are often started many years after the drugs were tested in adults and involve testing at arbitrary doses and schedules on the basis of scaled down versions of those used in adults. By this time the drugs are already off-patent and the financial incentive for the pharmaceutical company to be involved in this phase of development will have lapsed.[5] For oral drugs, a formulation suitable for very young children who are unable to swallow tablets or capsules is often unavailable. This unavailability means clinicians have had to improvise the administration of such drugs to these children, with unknown pharmacokinetic consequences. Finally, although clinical

Figure 1: Children receiving cancer treatment at the University of Modena and Reggio Emilia, Modena, Italy

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TEDDY Task-force in Europe for Drugs Development for the Young

Succesful Networking activities

Networking & Unmet Therapeutic Needs

Information on

1- drugs currently used off label for treating children with rare diseases

2- existing studies supporting the M.A.

Preliminary Results

1- drugs population 443 (used in children)

2- drugs used off-label for rare diseases

n° 37

3- conditions for which the drugs are used

n° > 100

4- paediatric studies at the M.A.

17 products/28 evaluated

DRUGS	AUTHORIZED INDICATION	OFF LABEL USE
ADALIMUMAB (HUMIRA 40 MG PHIAL)	RHEUMATOID ARTHRITIS, PSORIATIC ARTHRITIS	BEHÇET'S SYNDROME: SARCOIDOSIS (EARLY ONSET); WEGENER'S GRANULOMATOSIS
AMILORIDE	IN ASSOCIATION WITH IDROCLOROTIAZIDE (MODURETIC), THE AMILORIDE IS RECOMMENDED IN TREATING PATIENTS AFFECTED BY CARDIAC EDEMA, HEPATIC CIRRHOSIS WITH ASCITES, HYPERTENSION.	BARTTER SYNDROME, GITELMAN SYNDROME (PRIMITIVE HYPEALDOSTERONISM); NEPHROGENIC DIABETES INSIPIDUS, LIDDLESYNDROME
ANAKINRA	RHEUMATOID ARTHRITIS	SYSTEMIC AUTOINFLAMMATORY DISEASES FAMILIAL PRIMARY AMYLOIDOSIS
AZATHRIOPINE (CPR 50 MG)	TRANSPLANTS, RHEUMATOID ARTHRITIS, INFLAMMATORY INTESTINAL DISEASES, SYSTEMIC LUPUS ERYTHEMATOSUS, DERMATOMYOSITIS; POLYMYOSITIS; AUTOIMMUNE CHRONIC HEPATITIS; PANARTERITIS NODOSA; AUTOIMMUNE HEMOLYTIC ANEMIA; IDIOPATHIC THROMBOCYTOPENIC PURPURA	BEHÇET'S SYNDROME; SCLERODERMA; NEPHROTIC SYNDROME
BOSENTAN	PRIMITIVE PULMONARY HYPERTENSION	PROGRESSIVE SYSTEMIC SCLEROSIS
CYCLOFOSFAMIDE	ANTIBLASTIC CHEMOTHERAPY DRUGS	DERMATOMYOSITIS WEGENER'S GRANULOMATOSIS CHURG-STRAUSS SYNDROME MICROSCOPIC POLYANGIITIS
DRUGS	**AUTHORIZED INDICATION**	**OFF LABEL USE**
CICLOFOSFAMIDE (Endoxan 50 mg tables, 500 mg phial, phial)	CYTOSTATIC TREATMENT	SCLERODERMA; WEGENER'S GRANULOMATOSIS; MIXED CRYOGLOBULINEMIA; BEHÇET'S SYNDROME
CLOROCHINE (CLOROCHINE 250 MG TBL)	MALARIA PROPHYLAXIS AND TREATMENT, EXTRAINTESTINAL AMEBIASIS, IF NITROIMIDAZOLIC COMPOUND ARE NOT RECOMMENDED OR HAVE NO EFFECTS. RHEUMATOID ARTHRITIS (CHRONIC POLYARTHRITIS), INCLUDING JUVENILE TYPES. CHRONIC DISCOID LUPUS ERYTHEMATOSUS, SYSTEMIC LUPUS ERYTHEMATOSUS	DERMATOMIOSITIS, MIXED CONNETTIVE TISSUE DISEASE (PEDIATRIC ONSET)
COLCHICINE (COLCHICINE LIRCA 1 MG TBL)	GOUT	BEHÇET'S SYNDROME

Rare-Uses &Trials-Database: ISS WP leader

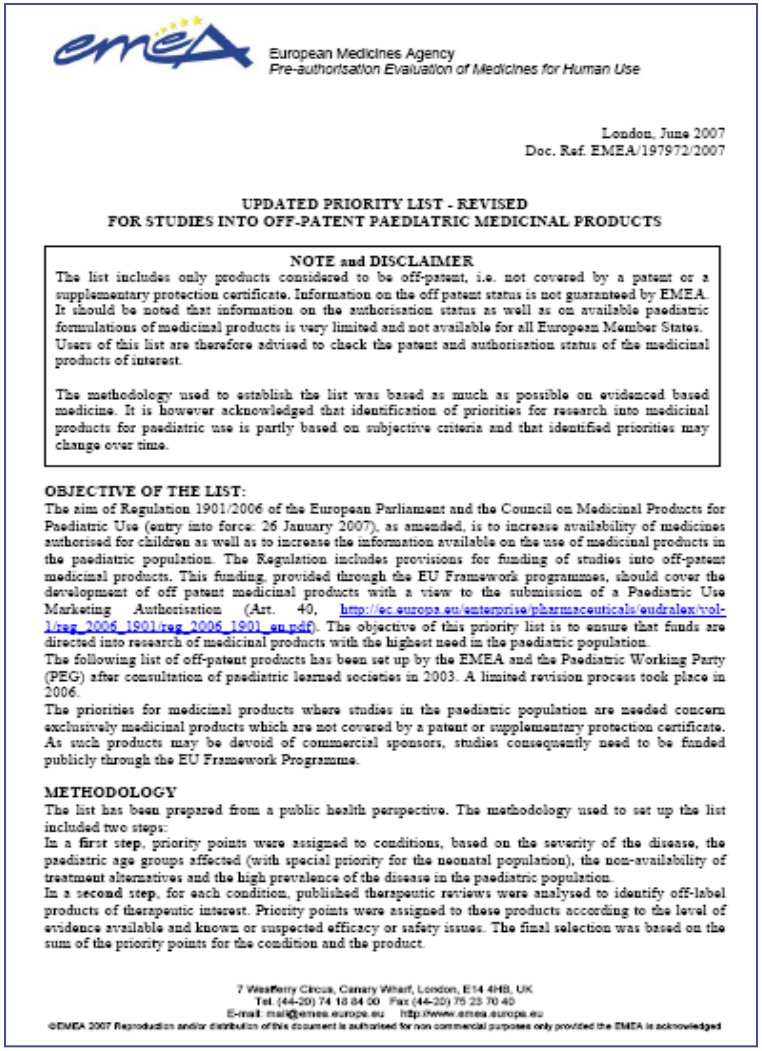
Community 7th Framework Program Cooperation-Health

Paediatric medicinal products

HEALTH-2007-4.2-1: Adapting off-patent medicines to the specific needs of paediatric populations

(next deadline: September 2009)

Support given to studies dedicated to provide evidence for specific paediatric use of off-patent medicinal products as included in the **EMEA-PDCO priority list** of Off-Patent Medicinal Products



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, June 2007
Doc. Ref. EMEA/197972/2007

UPDATED PRIORITY LIST - REVISED
FOR STUDIES INTO OFF-PATENT PAEDIATRIC MEDICINAL PRODUCTS

NOTE and DISCLAIMER

The list includes only products considered to be off-patent, i.e. not covered by a patent or a supplementary protection certificate. Information on the off patent status is not guaranteed by EMEA. It should be noted that information on the authorisation status as well as on available paediatric formulations of medicinal products is very limited and not available for all European Member States. Users of this list are therefore advised to check the patent and authorisation status of the medicinal products of interest.

The methodology used to establish the list was based as much as possible on evidenced based medicine. It is however acknowledged that identification of priorities for research into medicinal products for paediatric use is partly based on subjective criteria and that identified priorities may change over time.

OBJECTIVE OF THE LIST:

The aim of Regulation 1901/2006 of the European Parliament and the Council on Medicinal Products for Paediatric Use (entry into force: 26 January 2007), as amended, is to increase availability of medicines authorised for children as well as to increase the information available on the use of medicinal products in the paediatric population. The Regulation includes provisions for funding of studies into off-patent medicinal products. This funding, provided through the EU Framework programmes, should cover the development of off patent medicinal products with a view to the submission of a Paediatric Use Marketing Authorisation (Art. 40, http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf). The objective of this priority list is to ensure that funds are directed into research of medicinal products with the highest need in the paediatric population.

The following list of off-patent products has been set up by the EMEA and the Paediatric Working Party (PEG) after consultation of paediatric learned societies in 2003. A limited revision process took place in 2006.

The priorities for medicinal products where studies in the paediatric population are needed concern exclusively medicinal products which are not covered by a patent or supplementary protection certificate. As such products may be devoid of commercial sponsors, studies consequently need to be funded publicly through the EU Framework Programme.

METHODOLOGY

The list has been prepared from a public health perspective. The methodology used to set up the list included two steps:

In a first step, priority points were assigned to conditions, based on the severity of the disease, the paediatric age groups affected (with special priority for the neonatal population), the non-availability of treatment alternatives and the high prevalence of the disease in the paediatric population.

In a second step, for each condition, published therapeutic reviews were analysed to identify off-label products of therapeutic interest. Priority points were assigned to these products according to the level of evidence available and known or suspected efficacy or safety issues. The final selection was based on the sum of the priority points for the condition and the product.

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CONCLUSIONS

- **Networking** in the Paediatric Research sector is well accepted and represent an useful tool to increase medicines for children and to foster interdisciplinary research
- In the next few years many efforts will be needed to meet the paediatric regulation expectancies
- All actors, including **Academy and Industry**, are expected will participate in a collaborative, non competitive manner
- All available Financial sources as FP7 or IMI or National surces should be appropriately used to this aim

TEDDY contribution

- Paediatric Network in Europe are asked to provide scientific, regulatory, administrative and ethical support in order to:
  - **Prepare and submit appropriate Paediatric Investigation Plans (PIPs)**
  - **Provide Paediatric Pharmacovigilance and Risk Management Plans**
  - **Prepare and submit PUMA applications.**
  - **Conduct clinical trials and other studies of medicinal products in children in compliance with EU legislation**
- The existing TEDDY experience could facilitate these efforts