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Recommendation for drug development for children

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One of TEDDY objectives is to "to identify unmet therapeutic needs for the development and use of medicinal products in male/female children" and it is compliant with the new provisions established by the Paediatric Regulation.

Thus TEDDY set up 12 Therapeutic Experts Groups (TEGs) to identify the needs in some therapeutic areas of paediatric interest.

Starting from the Assessment Documents released by EMEA-PEG and later on by EMEA-PDCO, a total of 14 therapeutic areas were analysed.

TEDDY experts have identified 442 products that need to be specifically developed for children by either extending the current authorised indication or developing new indications. Moreover, the study shows that a total of 1480 studies (i.e. PK, dosage, efficacy, safety or long term safety) should be conducted in order to develop more drugs for children.

In the light of these results, it is reasonable to question if all these studies are absolutely necessary and consequently if there are enough children to be enrolled in the trials for the same therapeutic area.

It is imperative to adopt a procedure of selecting which drugs need to be developed for each therapeutic area in order to avoid repetitive and unnecessary trials in children.

Keywords: TEDDY, children, drug development, therapeutic needs, priority lists

1. Introduction

The Paediatric Regulation [16], entered into force in January 2007, establishes several obligations and incentives to stimulate and increase the number of medicines devoted for children.

One of the main pillars of the Paediatric Regulation is represented by the setting up of an inventory of the therapeutic needs of the paediatric population, as established by the Paediatric Committee (PDCO) after consultation with the Commission, the

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Table 1
TEDDY Therapeutic Experts Groups (TEGs)

1	Haematology/Oncology
2	Infectious Diseases
3	Immunology
4	Rheumatology
5	Neurology-Neuromuscular and psychiatric diseases
6	Gastroenterology
7	Respiratory
8	Cardiology
9	Nephrology
10	Diabetes
11	Pain
12	Formulation

Member States and interested parties. The inventory, to be regularly update, will identify the existing medicinal products used by the paediatric population and highlight the therapeutic needs and the priorities for research and development. In this way, companies should be able easily to identify opportunities for business development; the PDCO should be able to better judge the need for medicinal products and studies when assessing draft paediatric investigation plans, waivers and deferrals; and healthcare professionals and patients should have an information source available to support their decisions as to which medicinal products to choose.

In this framework, one of TEDDY objectives is to "to identify unmet therapeutic needs for the development and use of medicinal products in male/female children" and a specific Work Package (WP4 – Addressing key therapeutic questions in children) has been devoted to achieve this aim.

2. TEDDY therapeutic expert groups

Twelve Therapeutic Experts Groups (TEGs) (Table 1), formed by both internal and external experts and including different expertises (clinicians, clinical trial scientists, paediatric pharmacologists and clinical methodology researchers, etc.) were set up in order to achieve WP4 main objective: "to address questions concerning therapies in children with different chronic and acute diseases".

The groups concentrated their activities on systematically analysing, supporting and providing additional information to EMEA Paediatric Working Party (PEG) and PDCO lists of therapeutic need assessment, and in particular:

- giving opinion and possibly consensus (giving support) to the list of needs proposed by the PEG/EMEA;
- giving opinion on the type of paediatric clinical studies (as indicated by the PEG) that should be performed;
- providing, on the basis of all available scientific evidence, additional proposals to complete or modify the list;

Table 2
National and European Scientific Societies collaborating with TEDDY

SIOP Europe
European Paediatric Cardiology Association (AEPC)
European Society for Paediatric Endocrinology (ESPE)
European Society for Paediatric Infectious Diseases (ESPID)
European Respiratory Society (ERS)
Società Italiana per le Malattie Respiratorie Infantili (SIMRI)
European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)
Gastro-Intestinal Committee of the ESPGHAN
Società Italiana di Pediatria (SIP)

– increasing awareness on the assessments also through consultation with external experts.

Every issue related to the difficulties in R&D of paediatric medicines intended for a specific therapeutic indication (i.e. PK, safety, tolerability, efficacy, new formulation/different dosage, *etc.*) is highlighted.

TEDDY Experts have proceeded in identifying for each therapeutic area the existing products authorised for adult use and not for paediatric use or for other paediatric age categories.

In setting up the groups, *multidisciplinarity* was taken into account and for this reason experts groups were composed by clinicians, trialists, paediatric pharmacologists, methodologists, pharmacists, statisticians, academics, researchers. In this perspective, each TEG leader worked in order to guarantee the presence of every area of expertise. Up to now, more than 100 experts have been involved in the work of the TEGs.

TEDDY TEGs also made use of the cooperation of National and European Scientific Societies (Table 2).

2.1. Work methodology

The starting point of work for each TEG was the documents on therapeutic needs assessment released by the EMEA Paediatric Working Party (PEG) and Paediatric Committee (PDCO). The Experts Groups were asked to comment and also provide new suggestions on the documents released for consultation by the EMEA [1–15].

Moreover, for some therapeutic areas drugs available on the marketplace from Countries of the TEDDY Partners (Europe and Israel) were identified with particular reference to:

– drugs authorised under the Centralised Procedure and broken down for the above cited therapeutic areas (October 1995 – September 2005). For this group of drugs, representing the new and innovative medicines authorised by the EMEA, it is possible to collect a set of information easily available.
– drugs selected by PEG and PDCO and broken down for the above cited therapeutic areas. This group includes drugs authorised under National or Mutual recognition Procedures.

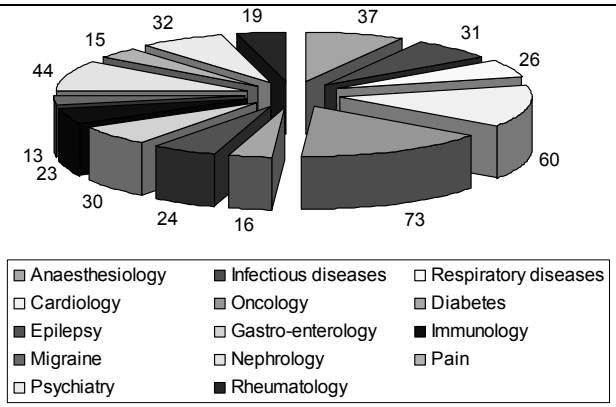


Fig. 1. Distribution of the selected products by therapeutic areas.

2.2. Experts evaluation

Expert groups of clinicians, clinical trial scientists, paediatric pharmacologists and clinical methodology researchers (TEDDY experts) were required to agree on a list of priority needs in key paediatric areas, and to make recommendations to Regulatory Agencies and sponsors.

In details each expert groups provided comments and suggestions on the docs above cited (EMEA PEG/PDCO Therapeutic Needs Assessment) in order to categorise and prioritise the therapeutic needs not covered by authorised treatment for children.

To better categorise the conditions/diseases treated by the examined drugs, the following classification was adopted:

- priority 0 = no interest for children since the drug is indicated for diseases which do not affect children;
- priority 1 = low priority for children since the drug is indicated for unserious diseases which affect both adults and children or diseases already cured in children;
- priority 2 = high priority for children since the drug is indicated for serious diseases which affect children and of which significant benefit compared with the existing methods could be derived by a new treatment.

3. Results

TEDDY experts have identified 443 products that need to be specifically developed for children in terms of extending the current authorised indication from adults to children or from older to younger children or in terms of developing new indication. A total of 14 therapeutic areas were analysed as shown in Fig. 1.

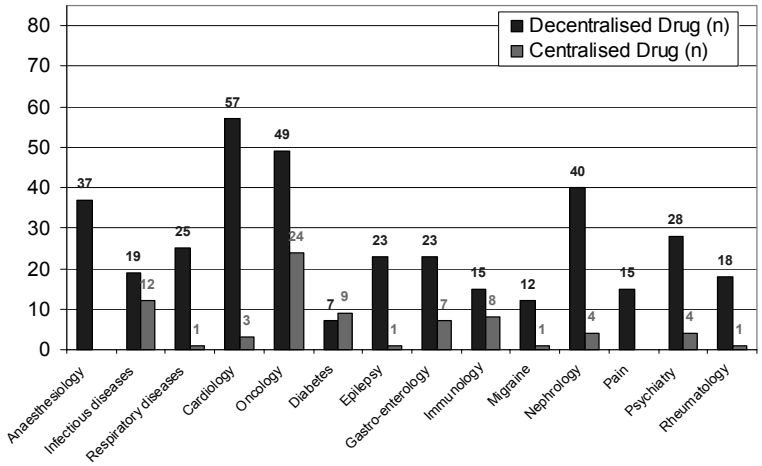


Fig. 2. Decentralised and Centralised products by therapeutic areas.

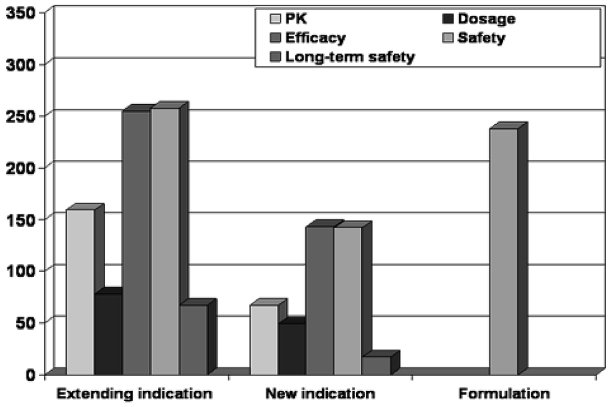


Fig. 3. Type of study requests by extending indication or new indication or formulation.

On a total of 443 products, 75 were products authorised under centralised procedure. The distribution of drugs both authorised under Centralised and Decentralised (National and/or Mutual recognition) procedures is shown in Fig. 2.

A total of 1473 studies are requested in order to develop products of paediatric interest. The details of the type of studies requested (PK, dosage, efficacy, safety or long term safety) are shown in Fig. 3.

Tables 3 and 4 include details of the products by therapeutic areas, Table 5 includes details on requests related to age appropriate formulations.

To better categorise the conditions/diseases treated by the examined drugs, experts provided a sort of classification, identifying the priority of research in a sample of

Table 3
Requests of studies by therapeutic areas for developing new indications

Therapeutic classes	Drugs (n)	PK	Dose	Efficacy	Safety	Long-term safety
Anaesthesiology	2			1	1	
Infectious diseases	2	1		1	1	
Respiratory diseases	16	5	1	16	14	
Cardiology	7		7	7	7	
Oncology	32	25	8	29	29	
Diabetes	1	1		1	1	
Epilepsy	5		2	5	5	
Gastro-enterology	20	6	7	19	20	5
Immunology	14	4	6	11	11	
Migraine	2		2	2	2	
Nephrology	29	21	8	29	29	1
Pain	1			1	1	
Psychiatry	9	4		9	9	5
Rheumatology	12		8	12	12	6
Total	152	67	49	143	142	17

Table 4
Requests of studies by therapeutic areas for extending current authorised indications

Therapeutic classes	Drugs (n)	PK	Dose	Efficacy	Safety	Long-term safety
Anaesthesiology	26	12	4	12	14	4
Infectious diseases	28	24		27	27	2
Respiratory diseases	19	5	11	16	17	9
Cardiology	52	2	41	44	43	6
Oncology	44	26		35	35	1
Diabetes	16	12		15	15	4
Epilepsy	15	11	3	8	9	2
Gastro-enterology	18	12	1	16	16	2
Immunology	12	2	5	8	8	3
Migraine	11	10		10	10	10
Nephrology	26	16	7	25	26	4
Pain	15	9	1	12	12	4
Psychiatry	25	18	2	23	23	15
Rheumatology	4		3	4	3	1
Total	311	159	78	255	258	67

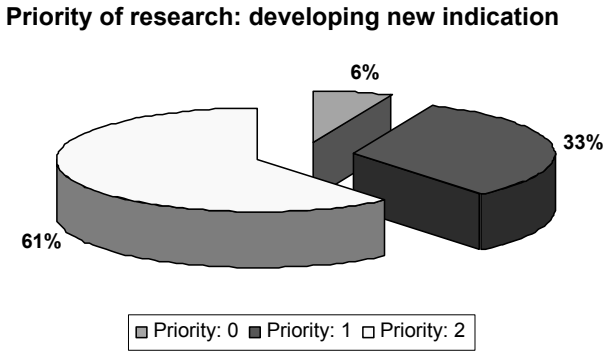
drugs as shown in Errore. L'origine riferimento non è stata trovata. and Fig. 5, according to the need of developing new indications and extending the current authorisation to paediatric populations.

4. Conclusions

The work carried out by the TEDDY TEGs shows that many studies are currently requested to develop more drugs for children.

Table 5
Requests of studies by therapeutic areas for developing age appropriate formulations

Therapeutic classes	Drugs (n)
Anaesthesiology	21
Infectious diseases	15
Respiratory diseases	8
Cardiology	50
Oncology	18
Diabetes	4
Epilepsy	17
Gastro-enterology	21
Immunology	11
Migraine	7
Nephrology	30
Pain	7
Psychiatry	15
Rheumatology	14
Total	238



Legend: Priority 0 = no interest for children since the drug is indicated for diseases which do not affect children; Priority 1 = low priority for children since the drug is indicated for unserious diseases which affect both adults and children or diseases already cured in children; Priority 2 = high priority for children since the drug is indicated for serious diseases which affect children and of which significant benefit compared with the existing methods could be derived by a new treatment.

Fig. 4. Priority of research as defined by TEDDY experts (new indications) in a sample of 71 drugs.

More clinical trials will have a positive effects on drug rationale use and on ADRs reduction in children. On the other hand, it is reasonable to question if all these studies are absolutely necessary and consequently, if there are enough children to be enrolled in the trials for the same therapeutic area.

Our study demonstrates that it is necessary to apply specific criteria to select

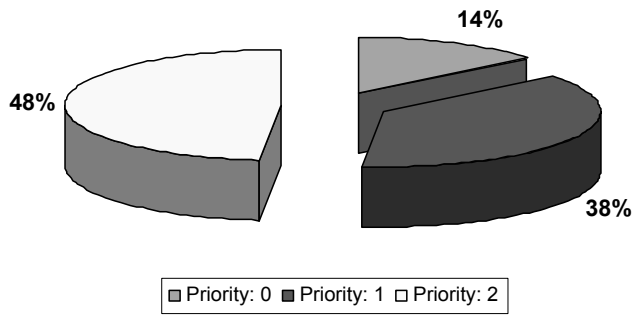


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Fig. 5. Priority of research as defined by TEDDY experts (extending indications) in a sample of 148 drugs.

the medicinal products for which developmental efforts are absolutely needed and that through these criteria it will be possible to reduce the economic and research commitment by 6–14% (priority 1 and 2 studies only) up to 33–38% (priority 1 studies only).

A first reduction can be performed by selecting drugs belonging to the same therapeutic area and having the same level of interest of which only the more interesting should be proposed to be investigated and developed in children.

Moreover, integrating the results of this study with what emerged from the analysis carried out by TEDDY on the existing paediatric clinical trials (both registrative and non-registrative), we can demonstrate that good quality paediatric studies already exist for many active substances included in the therapeutic needs lists, thus they should not be repeated in vain. This also represents a criterion.

In conclusion, to define priorities TEDDY suggests the adoption of at least the following criteria:

- the lack of any paediatric alternative treatments on the market;
- the existence of therapeutic interest relevant for paediatrics;
- the lack of evidences from paediatric clinical studies supporting the marketing authorisation of the currently available drugs used in children.

This selection criteria should be adopted not only by Pharmaceutical Companies, but also in European and National Research Programs in order to better concentrate

public and private efforts on those drugs lacking of a specific indication for children and also of paediatric studies.

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