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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Medicines for children licensed by the European Medicines Agency (EMEA): the balance after 10 years

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Abstract
Objective The 1995–2005 balance of EMEA activities in the field of paediatric medicines was evaluated, taking into account the number both of drugs authorised for children and paediatric studies supporting the Marketing Authorisation (MA).
Methods Data on drugs authorised by EMEA were extracted from EPARs (European Public Assessment Reports). Active substance, year of approval, anatomical, therapeutic and chemical (ATC) code, indication, orphan status, ages, and registrative clinical studies characteristics were assessed.
Results The percentage of authorised substances for paediatrics is 33.3%. This percentage decreased or increased when different subsets of medicines were considered [medicines for children under 2 years (23.4%), N-ATC code drugs (6%) and orphan drugs (46.4%)]. A total of 165 trials were included in the MA dossiers of 51 drugs at the time of approval, and additional 22 studies were added to the dossiers of 12 active substances submitted for paediatric variations. PK and Efficacy/Safety studies were performed for 32 (52%) active substances, while either one PK or one Efficacy/Safety study was carried out for 43 (69%) and 45 (73%) substances, respectively.
Conclusions This report demonstrates that the total number of paediatric medicines approved by EMEA is stable over the 10-year period, while an increase in drugs to treat serious or orphan diseases has been observed. In addition, under the Centralised Procedure, a valuable number of paediatric trials have been submitted to support drug approval.

Keywords EMEA · Marketing authorisation · Paediatrics

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Introduction

The main goal in the pharmaceutical field is to guarantee that efficacious, high quality and safe medicines are available to European citizens, regardless of income or social status. The proper use of medicines is dependent upon a wide dissemination of relevant information to all interested stakeholders (Regulatory Agencies, medical doctors, pharmacists, patient associations, industries, etc).

For many years, a lack of information on drugs continued to affect the paediatric population. It is well known that approved medicines are used in children

without proper information on: dosage, potential toxicity, evidence of clinical safety and efficacy at the recommended dosages [1, 2].

The specific issue of paediatric medicines has been considered by the European Institutions since 1997. For this purpose, a number of initiatives have been developed in the last few years: at the European Medicines Agency (EMEA), a Paediatric Working Party has been specifically set up, while the new Paediatric Regulation [14] is expected to be adopted within 2007.

The aim of this report is to discuss the 'state of the art' of paediatric medicines licensed by EMEA in the last 10 years.

In details, we evaluated the number and the characteristics of:

1. Medicines licensed for use in children by EMEA in the period October 1995–September 2005.
2. Paediatric studies supporting the Marketing Authorisation (MA).

Our analysis focused on new and innovative medicines authorised by EMEA, in the European marketplace, including the 'orphan drugs' subset, as defined by the Orphan Regulation no. 141/2000/EC [3]. In fact, children represent a large part of the population affected by rare diseases.

Methods

We examined the paediatric medicines registered in Europe under the EMEA Centralised Procedure (EMEA-CP) in the October 1995–September 2005 period, deriving information stored in the European Paediatric Medicines Database (EPMD) [2], set up in 1999 and currently managed under TEDDY NoE activities[1].

Data sources

a) European Public Assessment Reports (EPARs) available at the EMEA website (http://www.emea.eu.int);
b) The "Community register of medicinal products for human use" (http://www.pharmacos.eudra.org).

Data evaluated

For the purpose of this report the following parameters were assessed:

- Year of approval
- Active substance
- ATC code (first-level)
- Orphan status
- Indication
- Age for which the drug is intended
- Paediatric dosages
- Clinical studies supporting MA (number and characteristics of the experimental population, phase and types of the study).

Analysis

Descriptive statistics were performed in order to identify the paediatric medicines approved by: (1) year of MA, (2) age of population for which the drug is approved, (3) ATC code, (4) orphan status, and (5) number and type of paediatric clinical trials included in the MA documentation.

A comparative analysis between the present findings and those previously reported [2, 4] has been also carried out considering (1) the subset of paediatric medicines approved by EMEA during the first five years of activity, and (2) the subset of paediatric medicines approved through the Italian national or decentralised procedure.

Definitions

1. *Paediatric medicines*: medicines with registered labels including information to allow paediatric use. The inclusion of information about both label and Package Leaflet[2] (PL) were related to paediatric indication and dosage (by age(s) and/or by weight).
2. *Paediatrics age groups*: the groups of ages defined according to the ICH Topic E11 'Clinical Investigation of Medicinal Products in the Paediatric Population' Guideline (2000) [6].
3. *Paediatric clinical studies*: clinical studies in one or more paediatric age groups.
4. *Paediatric clinical trials characteristics*: the type and definition of clinical trials according to the ICH E8 Guideline criteria [7].
5. '*Orphan drugs*' and '*Orphan-like drugs*'[3]: as defined in the Regulation n. 141/2000/EC [3] and in the "Status Report on the implementation of the European Parliament Legislation on Orphan Medicinal Products" [8], respectively.

[1] TEDDY is a EU funded project aimed at favouring the development and the rationale use of drugs for the paediatric population.

[2] the Label (labelling) is defined according to the DIRECTIVE 2001/83/EC (art.1) as the 'information on the immediate or outer packaging' while the 'Package leaflet' is 'a leaflet containing information for the user which accompanies the medicinal product' [5].

[3] Orphan-like drugs are drugs intended for patients with rare diseases, authorised prior to introduction of the "Orphan" legislation and for whom EMEA provided support in the form of fee reductions for post-authorisation activities [6].

Results

General aspects

In the period October 1995–September 2005, 314 medicinal products (MP) corresponding to 238 active substances (AS) have been approved by EMEA. Among these, 36 products (16 active substances) were withdrawn for safety and commercial reasons. Thus, in October 2005, 278 MP, corresponding to 222 AS, authorised under the Centralised Procedure were available in Europe.

Seventy-four out of a total of 222 AS include in their documentation (SPC/PL) information allowing paediatric use. In specific terms, 40 AS were granted both a paediatric indication and dosage, 25 AS only included a paediatric dosage, and for 9 AS, a dosage was given based on the body weight. The paediatric use was authorised at the MA time for 65 AS, corresponding to 47 MP (33%) in the period 1995–2001 and 18 (22%) in the period 2001–2005, and during variation procedures for 9 substances.

The number of paediatric medicines approved by year varied between 19% and 48%, with an average level of 33.3%.

The ages reported in the MA documentation (Table 1) are a wide range and only rarely correspond to the five age categories as stated in the ICH E11 Guideline [6]. The number of medicines approved for younger children is lower than those for older ones (the percentage being 9.4% and 23.4% in the newborn and in the infant groups, respectively) and in particular, only 7 active substances have been approved for newborns (6) and preterms (1). Just 16% (n=12) has been approved for all paediatric ages.

Table 1 Age for which the medicine is authorised

Age	No. active substances
Preterms	1
Newborns	6
	>2 months
2	
	>3 months
1	
	>4 months
1	
>1 year	10
>2 years	7
>3 years	8
>4 years	4
>5 years	3
>6 years	6
Children[a]	1
>10 years	1
>11 years	1
>12 years	8
>15 years	1
>16 years	1
All ages	12
Total	74

[a] Age not defined

ATC and orphan status

Paediatric medicines belong to 11 ATC first-level categories, two more ATC classes (cardiovascular and nervous system) than in the previous analysis [2]. The percentage of paediatric medicines for each therapeutic area significantly varies among ATC codes: as indicated in Table 2, J-ATC (anti-infectives for systemic use) represents the group with the highest ratio (68%) while N-ATC the lowest one (5%). Similar findings were obtained in 2001 research.

Table 2 also shows that among 21 orphans plus 7 orphan-like drugs licensed, 13 (9 orphans and 4 orphan-like) were approved for use in children. Noticeably, orphan paediatric drugs concentrate in 4 ATC categories: A (Alimentary tract and metabolism class) or C (Cardiovascular system), B (Blood and blood forming organs) and N (Nervous system) covering relevant paediatric needs in this area. Carglumic acid, nitisinone, laronidase, zinc acetate dehydrate, sodium phenyl butyrate, imuglucerase, cysteamine bitartrate and also bosentan, ibuprofen, levetiracetam are some examples of approved drugs.

Comparing the rate of paediatric medicines in orphan and non-orphan drug groups, we noted a significant difference in favour of paediatric medicines in the orphan drug group (46.4% vs 31.4%; p=0.13).

Paediatric clinical trials supporting marketing authorisation

A total of 187 paediatric trials were included in the MA dossier of 62[4] paediatric drugs, of which 165 were presented at the time of the MA and 22 during the extension procedures. Fifty-two were studies on clinical pharmacology (PK/PD/dose finding), 87 on efficacy and/or safety and 30 on PK/PD/efficacy/safety. The remaining were unclassified (4), compassionate (2) or bibliographic (12) (Table 3).

A breakdown by class of the trials related to active substances is shown in Table 3. Out of the total of 62 drugs, 61.3% were studied with at least 1–3 paediatric trials; and 29% with more than 3 studies. Twenty-nine active substances (52%) were investigated in trials enrolling only paediatric populations, ranging from 12 to 1,826 patients.

Forty-three percent of paediatric medicines had at least one PK study and 45 had at least one efficacy or efficacy/safety study, while 32 (52%) had both PK and efficacy/safety clinical studies included in their dossiers (Table 4). One product (imiglucerase) was approved with the support only of paediatric bibliographic data and 11 were approved

[4] Vaccines are excluded by the analysis.

Table 2 EMEA paediatric medicines by ATC code and orphan status

	Paediatric/total					Paediatric/total	
	1995–2001		2001–2005			1995–2005	
	n	%	*n*	Variations	%[a]	*n*	%
J–Anti-infectives for systemic use	24/34	71	4/10	2	60	30/44	68
A–Alimentary tract and metabolism	7/13	54	6/13	1	54	14/26[b]	54
L–Antineoplastic and immunomodulating agents	4/25	16	2/24	3	21	9/49[b]	18
B–Blood and blood forming organs	6/14	43	1/6	–	17	7/20[b]	35
R–Respiratory system	2/2	100	1/1	–	100	3/3	100
C–Cardiovascular system	0/3	–	2/5	–	40	2/8[b]	25
D–Dermatologicals	12	50	1/1	–	100	2/3	67
S–Sensory organs	1/3	33	1/2	–	50	2/5	40
H–Systemic hormonal preparations, excluding sex hormones and insulins	1/3	33	0/4	–	–	1/7	14
N–Nervous system	0/8	–	0/10	1	10	1/18	5
V–Various	1/16	6	0/16	1	6	2/16	12
All others ATC	0/18	–	0/5	1	20	1/23	4
Total	47/141	33%	18/81	9	33%	74/222[b]	33%

[a] Percentage calculated considering the drugs authorised in the period plus granted variations

[b] Including orphan and orphan-like drugs (paediatric orphans/total orphans): A: 7/10 (70%); L: 3/9 (33%); B: 1/2 (50%); C: 2/2 (100%); Total 13/28 (46%)

in spite of a lack of paediatric studies. For 6 of these AS, unstudied at the time of the MA, post-marketing paediatric studies were submitted during variation procedures while 5 medicinal products (abacavir/lamivudine, eflornitine, lamivudine/zidovudine, mitotane, repaglinide) are still marketed without paediatric research.

Comparative analysis

This analysis demonstrates that the total number of paediatric medicines approved by EMEA under the Centralised Procedure is stable over the 10-year period, while the number of covered therapeutic areas (ATC) increased from 9 to 11.

The percentage of paediatric medicines supported by paediatric trials also increased from 77% to 91%. The paediatric trial/paediatric medicine ratio is equal to 2.8 and 3 in the 1995–2001 and the 1995–2005 periods, respectively. These ratios increase to 3.6 and 3.3, respectively, if we consider the average number of paediatric clinical studies performed for each paediatric medicines whose MA documentation included paediatric trials (Table 5). Comparing these results with those obtained from our 2001 research, paediatric medicines and paediatric trials are significantly lower in the national/decentralised approved medicines group than in the centralized medicine groups (both periods). In addition, in this last group the number of therapeutic areas (ATC) in which paediatric medicines are approved is only five (Table 5).

Table 3 Paediatric clinical trials (type) reported in EPARs

TRIALS	No. at MA time	No. at variation time	Total	%
PK/PD/dose finding	47	5	52	27.8
Efficacy and/or safety	76	11	87	46.5
PK/PD/efficacy/safety	24	6	30	16.0
Other	4	0	4	2.1
Compassionate	2	0	2	1.1
Bibliographic PK/efficacy/safety	12	0	12	6.4
Total	165	22	187	100

Table 4 Paediatric clinical trials characteristics

Number of studies for one active substance	Number of active substances	%
1–3 studies	38	61.3
More than 3	18	29.0
No studies	5	8.1
Bibliographic only	1	1,6
Total	62	100
Characteristic of study population		
Paediatric	29	51.7
Paediatric and adults	24	42.8
Not provided	3	5.5
Total	56	100
Type of study		
None	5	8.1
Bibliographic	1	1.6
PK alone or other phase 1–2 studies	11	17.7
PK/efficacy/safety	32	51.6
Efficacy alone or other phase 3 studies	13	21.0
Total PK	43	69.4
Total efficacy	45	72.6

Table 5 Comparative analysis between drugs approved under Centralised and Non-Centralised (National and Mutual Recognition) procedures

	National/MR (1995–2001)		EMEA (1995–2001)		Total EMEA (1995–2005)	
Paediatric medicines/total medicines	19/143	12%	47/141	33%	74/222	33%
ATC covered in paediatrics	5/14	35%	9/14	64%	11/14	78%
Paediatric medicines supported by paediatric trials/paediatric medicines	5/19	26%	28/36	77%	57/62	91%
Paediatric trials/paediatric medicines	8/19	ratio=0.4	101/36	ratio=2.8	187/62	ratio=3
Paediatric trials/paediatric medicines with paediatric trials	8/5	ratio=1.6	101/28	ratio=3.6	187/57	ratio=3.3

Discussion

After 10 years of EMEA activity, the number of paediatric medicines approved in Europe has not significantly increased compared with the past [2, 9], and many new or innovative approved drugs are still denied to children of different age groups and in different clinical–therapeutic categories.

In particular, the percentage of medicines for the paediatric population is 33.3% of total EMEA drugs. This figure falls to 9.4% and 23.4% in the newborns and in the infants groups, respectively. Our data also demonstrate that the age for which the drug is indicated is not compliant with the five age categories listed in the ICH E-11 guideline [6]. However, it varies case by case, leading to both an increase in therapeutic errors and an actual difficulty in correctly prescribing drugs and avoiding possible 'off-label' use [10–12].

Only 51% of products were approved after an adequate paediatric development plan completed at the MA time.

Notwithstanding this disappointing situation, a positive trend can be observed in the approval of paediatric medicines referred to some therapeutic areas (i.e. neurology, cardiovascular) of great paediatric interest. In particular, if we consider orphan diseases, the percentage of medicinal products available for children rises to 46.4%, in comparison with the 31.4% in the non-orphan drugs group.

Only few years ago, an Eurordis report underlined that "quofor designated orphan drugs, of which 66% have an indication exclusively for children or both for children and adults, very few sponsors are submitting data from paediatric studies when requesting marketing authorisation or raising specific questions on paediatric populations when requesting protocol assistance" [13].

In light of our results, the lack of medicines in the orphan drug field seems to be progressively overcome suggesting that the adoption of a legal instrument (i.e. the recently European Parliament approved - 2nd reading - Paediatric Regulation [14]) could fill in the gap of paediatric medicines in other fields as the Orphan Regulation no. 141/2000/EC is doing in the orphan drugs field.

A second relevant result of our analysis is the increased number of paediatric medicines approved on the basis of well performed paediatric trials. In fact, 91% of the examined products includes paediatric data in their registrative documentation, while in our previous reports [2, 4], only 77% of the products approved under the centralised procedure and less than 25% of those approved under the decentralised procedure were approved on the basis of paediatric data [4].

In particular, the current evaluation has demonstrated that almost one-third of the active substances were approved on the basis of a satisfactory drug developmental plan including PK/PD/Efficacy/Safety paediatric studies with a trials/ medicines ratio varying from 3.3 to 3.6. This is of particular interest because, up to now, with the lack of any ad hoc paediatric regulation, a percentage of between 50% and 90% medicinal products used in children in Europe have never been specifically studied in paediatrics and, when studied, the number of paediatric clinical trials included in the MA dossier has been very limited [1, 2, 4, 13, 15]. Moreover, in only few cases has a whole developmental paediatric plan been performed.

In conclusion, since the implementation of the Centralised Procedure, a positive trend in the approval of safe and efficacious medicines for children seems to be in progress in Europe. This trend is expected to increase rapidly in the future as a result of paediatric initiatives set up by EMEA and the European Commission, in particular the proposed Paediatric Regulation.

Following the US initiatives [16, 17], the EU Regulation specifically aims at increasing the Europe-wide availability of high quality medicines tailored to children. Manufacturers will be required to carry out research on the basis of a Paediatric Developmental Plan, to be initially approved by a new EMEA Paediatric Committee. Incentives for pharmaceutical companies and the facilitation of scientific advice procedures will favour the new Regulation applica-

tion. It will also favour drug availability, through an ad hoc paediatric registry of information about paediatric completed and on-going clinical trials in Europe and worldwide. Finally, extra funding will be available and used to consolidate existing paediatric research centres to deliver faster progress in developing drugs for use in children.

Conclusions

The establishment of EMEA has induced many effects on the pharmaceutical system in terms of approval of innovative, high quality medicines. Until now, the paediatric population has been only partially advantaged in terms of paediatric medicines appropriately studied and available to be used in children in a safe and effective manner.

Nevertheless, this report demonstrates that in the 10 years of EMEA activity an increased number of well studied paediatric medicines has been approved in therapeutic areas of relevant interest and, notably, in the orphan diseases field. This result is of particular value because it demonstrates that the lack of medicines in specific sectors can be overcome if an ad hoc European policy is adopted.

Furthermore, despite the lack of an ad hoc Paediatric Regulation, when applying for Centralised Procedure MA more paediatric studies are included in the MA dossier. This is creating a relevant mass of paediatric data which should also be analysed in order to select and circulate models and methodology of clinical trials that appear to be particularly suitable for use in children.

Notwithstanding, in the framework of a Paediatric regulation, a crucial aspect will be represented by the need to demonstrate that paediatric trials included in the MA dossiers provide conclusive evidence and that they do not constitute just a way of benefitting the incentives established for manufacturers [18, 19].

In conclusion, in this perspective, the new Paediatric Regulation [14] should play a role not only in increasing the number of paediatric medicines but also in guaranteeing high level paediatric trials in Europe.

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