Abstract **Objective:** The aim of this study was to evaluate the number and the characteristics of medicines approved for children in Europe by the European Agency for the Evaluation of Medicinal Products (EMEA) and whether the paediatric studies supporting the authorisation were in accordance with the *Note for Guidance on the Clinical Investigation of Medicinal Products in children* (CPMP/ICH/2711/99). We also considered any possible difference between the EMEA and the Food and Drug Administration (FDA) paediatric medicines evaluations.

**Methods:** We examined the drugs authorised by the EMEA through the centralised procedure from January 1995 to September 2001 deriving information from the “European Medicines – Database” (EMD) set up in 1998 by the Italian Group for Pharmacoeconomic Studies (GISF) and sponsored by the Italian Ministry of Health. The analysis of paediatric data has been managed by experts belonging to the Clinical Pharmacology Working Group of the Italian Paediatric Society. The following parameters were assessed: active substance, year of approval, anatomical therapeutic and chemical (ATC) code, therapeutic indications, age for which the drug is authorised, interest to children and paediatric studies supporting a paediatric authorisation. European Public Assessment Reports (EPARs) were considered as reference sources.

**Results:** The median percentage of drugs authorised for children from 1995 to 2001 (September) is 35% of the total of commercially available drugs; only 16 medicines have been approved for children under 2 years of age (11%), ten of these being vaccines. Medicines for children shared out 9 ATC classes, 24 belonging to the J-(anti-infective agents) -ATC class. Thirty-nine medicines were authorised on the basis of at least one clinical trial (27 phase III, 6 phase II, 6 phase I) while eight active substances have been licensed without any paediatric investigation.

**Conclusions:** Under the EMEA centralised procedure, several active substances have been licensed for children. Consequently serious and life-threatening diseases as AIDS and diabetes are now treatable, in a legal framework overcoming the orphan status of the past years. Despite the reported encouraging results, the number of drugs devoted to children remain low and important ATC classes, as L-(oncology) or N-(neurology), are still ‘orphans’ of innovative medicines. At the same time few medicinal products are specifically studied in children. Consequently, more efforts have to be made to increase the number of drugs assessed and licensed for the paediatric population, and manufacturers should be required to supply data on the effects of new drugs in children when the products are expected to offer a benefit over existing therapies.

**Keywords** Children · European Community · Licensed medicines · Clinical studies

**Introduction**

For many years, because of the lack of studies specifically designed to investigate pharmacological and toxicological aspects in paediatric populations, many approved drugs have been used in children without proper information on dosage and potential toxicity [1, 2, 3] or without appropriate dosage forms.
Consequently, marketed drugs have frequently been used off-label [4, 5, 6, 7] or unlicensed drugs have been employed. This attitude seems to lead to an increased rate of adverse drug reactions and medication errors [6, 8, 9, 10].

To provide adequate information on paediatric use of medicinal products, the Food and Drug Administration (FDA) developed a number of initiatives (1994: Pediatric Labeling Rule [11]; 1997: FDA Modernization Act-FDAMA, Section 111 [12]; 1998: Mandatory Paediatric Rule [13]) giving incentives and obligations to the pharmaceutical industries for conducting paediatric studies.


European initiatives, in contrast with those of the FDA, excluding incentives and obligations, simply encourage the companies to investigate drugs in children with the hope that they would result in a change of attitude by pharmaceutical industries. The aim of the present study was to evaluate the number and the characteristics of medicines approved for children in Europe by the EMEA as well as the number and types of paediatric studies supporting authorisations.

The medicines approved under the EMEA centralised procedure represent a homogeneous sample of medicines useful for this purpose because (a) the centralised procedure is devoted to innovative drugs for the care of serious and/or untreatable diseases, (b) the essential documents used for the marketing authorisation are currently available and published as European public assessment reports (EPARs) in the EMEA database and (c) a single high-level committee is responsible to give scientific advice for planning clinical studies. In our analysis we also took into account any possible existing difference between the EMEA and FDA paediatric medicines status and evaluations.

**Methods**

We examined the drugs authorised by the EMEA through the centralised procedure from 1995 to September 2001, deriving information from the ‘European Medicines – Database’ set up in 1998 by the Italian Group for Pharmacoeconomic Studies (GISF) [19] and sponsored by the Ministry of Health with the aim of collecting information on new and innovative medicinal products marketed in Europe. EPARs have been considered as reference sources.

EPAR reflects the scientific conclusion reached by the Committee for Proprietary Medicinal Products (CPMP) at the end of the evaluation process for marketing the product. It is made available by the EMEA for information to the public after deletion of commercially confidential information. The content of the EPAR summarises the various reports produced during the centralised evaluation procedure, resulting from the review of the documentation submitted by the applicant together with the scientific discussion. It also contains a summary of product characteristics and the information to be included in the patient information leaflet.

The following parameters were assessed:

- Active substance
- Year of approval
- Anatomical therapeutic and chemical (ATC) code
- Therapeutic indication
- Age/s for which the drug is authorised
- Clinical studies leading to paediatric authorisation

According to CPMP/ICH/2711/99, the ages for which the drug is intended are defined in completed days, months, or years as follows:

- New-born infants (0–27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2–11 years)
- Adolescents (12–17 years)

For the purposes of our analysis, we considered four categories of drugs according to the severity and for interest in treating diseases for children:

- Category 0 = drugs for diseases that do not affect children
- Category 1 = drugs for non-serious diseases that affect both adults and children or diseases already cured in children
- Category 2 = drugs for serious diseases that affect children and of significant benefit compared with the existing methods
- Category 3 = drugs for diseases still incurable in children

Category definition was done with the support of the Clinical Pharmacology Working Group set up by the Italian Society of Paediatrics. Clinical trials were defined according to the phase of the study (I, II or III) and to the age of the experimental population.

For medicinal products approved by the FDA, we analysed each product information (PI) document. The PI is the package labelling reporting the product characteristics. It is written by the sponsor, approved by the FDA and used during all phases of drug development; it also contains the design and analysis of clinical trials that were planned to address and to support the proposed label. These documents are available on the World Wide Web (www.rxlist.com, www.micromedex.com). Data management and analysis were done using the Microsoft Access Office 2000 Software package.

**Results**

Since 1995 the EMEA has considered a total of 339 applications for drugs approval. CPMP has provided 217 opinions and 127 active substances, and 14 vaccines have been granted a community marketing authorisation. Of these, 47 (33%) are available for use in children, 10 with paediatric dosage forms and 23 with specific paediatric dosage.

As shown in Table 1: