

Medicines for Mankind

TODAY'S RESEARCH, TOMORROW'S CURES

MEDICINES FOR CHILDREN



EUROPEAN FEDERATION
OF PHARMACEUTICAL INDUSTRIES
AND ASSOCIATIONS

Introduction

A fifth of the total population of the European Union is younger than 16 years of age. In the European Union of 25 Member States, this represents about 100 million individuals.

As in adult populations, progress has been achieved in numerous paediatric therapeutic fields, thanks to medicines that provide cure or relief from diseases affecting children. For example, major achievements are reported in haematology, oncology, cardiac or renal transplantation, vaccination, or in the treatment of asthma, infectious diseases, neonatal respiratory distress, and HIV. Children's health has also been improved through pharmaceutical developments in treatment for conditions such as diabetes, neuropsychological dysfunctions, cystic fibrosis, or in the relief from pain.



However, a significant number of medicines prescribed to children have not been specifically developed or assessed for paediatric use¹. The lack of medicines suitably adapted to paediatric populations in Europe has been highlighted in various scientific, medical, political and public forums. The European Union Summit held in Nice in July 2000 brought this public health issue to the attention of Community officials.

All stakeholders with a potential role in ensuring that appropriately investigated medications are made available for children must work towards this common goal. This is true of Community institutions, national governments, regulatory authorities, the scientific and medical community, professional and patient organisations, academia, industry, and others.

The research-based pharmaceutical industry of the European Union, of which the EFPIA is the representative voice, is already playing an active role in improving pharmaceutical treatment for all members of society, including children of all ages. And it fully shares this goal of ensuring greater availability of medicines designed specifically for children.

This document presents the current status of paediatric therapies (Section I) and barriers to paediatric research (Section II), as well as a number of challenges to be faced by all parties involved, including the pharmaceutical industry (Section III).

Current status of paediatric therapies

A significant number of medicinal products, whether used in paediatric hospital wards or prescribed by general practitioners, have not been developed and assessed specifically for paediatric use, and are prescribed outside the terms of their product license ("off-label" prescribing). Due to the lack of acceptable formulations appropriate for their age and weight, children are exposed to the risk of adverse drug reactions, and are often unable to benefit from many of the therapeutic advances offered to adults.

Off-label use of medicinal products in children in the EU

Unlicensed and off-label² use of drugs in children are current concerns for the European Community. The high number of recently published surveys that have been conducted on this issue across the European Union attest to this³.

From hospital experience, it has been possible to identify the number of paediatric prescriptions for non-approved drugs or off-label use, according to local/national practice and by disease. Reported data illustrates the discrepancies observed with regard to the use of the right drug formulation (oral vs. parenteral, tablets vs. capsules⁴, categories of age (neonates are the most concerned at 65%), dosages, frequency or indication. Interestingly, information provided by these studies is consistent. As a representative example, a multinational study (UK, Sweden, Germany, Italy and Netherlands) has been published in the British Medical Journal⁵. The main outcomes were as follows:

“Over a period of 4 weeks, 2,262 prescribed drugs were administered to 624 children from 4 days to 16 years old in 5 hospitals. Thirty nine percent of the drugs were prescribed outside the terms of the product licence. Two thirds of the children (421; 67%) received an unlicensed or off-label drug prescription during their stay in hospital. The most common category of off-label drug use was dose and frequency, accounting for more than half of off-label use. Other major categories for off-label drug use were formulation and age”.

The picture in office-based practice is somewhat different to the one observed from hospital surveys. Off-label prescriptions are widespread while unlicensed drug use is less common than in hospital. Some differences between surveys and countries may be noted (33% of unlicensed or off-label use in France⁶, vs. 15% and 22% in UK⁷).

Safety of medicines for children

Tetracycline-induced dental dysplasia and neonatal deaths due to chloramphenicol-induced “grey baby” syndrome illustrate historical examples of untoward outcomes due to the absence of paediatric data.

More recently, a significant difference that has been observed between the hospitalisation rates in adults and children has been attributed to the greater range of unlicensed or less-informed use of drug therapies in children⁸. Similarly, the FDA examined hospitalisation rates for 5 serious illnesses (asthma, AIDS/HIV, cancer, pneumonia and kidney infections)⁹. In each case, hospitalisation rates were higher for children than for adults.

There is most evidence on adverse drug reactions (ADRs) relating to all drugs used in children, with little on those that stem from off-label or unlicensed use¹⁰. However, a recent study has suggested that the use of medicines in an unlicensed or off-label manner may be associated with a greater risk of ADRs than medicines used as stated in the product license¹¹.

Availability of paediatric formulations

Numerous drugs used for infants and children are not available in an acceptable formulation such as suitable liquid dosage forms¹². This is due to various considerations such as the difficulty of developing paediatric formulations. A recent document reports the results of a European survey of extemporaneous dispensing and importation practice for paediatric patients emphasising the need for paediatric formulations¹³.

Paediatric formulations are needed because:

- Most children under 6 years (and many older children) cannot swallow tablets;
- Appearance, smell and flavour can greatly effect compliance;



- Children do not have the co-ordination to use certain devices in the same way as adult patients, e.g., dry powder inhalers; and
- The limited muscle mass of children causes intra-muscular injections to be very painful.



Lack of appropriate paediatric formulations is one of the major reasons leading to off-label uses of drugs in children¹⁴.

Critical needs

The need for adequate paediatric products is particularly critical in such conditions as AIDS and cancer – but obviously this is only a sample of the medical needs of paediatric populations.

Development of medicinal products for the treatment of paediatric HIV infection is clearly of utmost importance. It must be seen in the context of the epidemiology information.

- By the end of year 2002, 42.0 million people were infected with HIV; the total worldwide number of children under 15 living with HIV/AIDS is estimated to be 3.2 million.
- The total worldwide number of children under 15 who were newly infected with HIV during 2002 was estimated to be 800,000.
- Over half a million children (610,000) died of AIDS in 2002.
- By the year 2000, worldwide, 21.8 million people had died of AIDS, and 4.3 million of them were children.

Continued efforts in the paediatric development of new and existing HIV infection therapies must be considered a priority.

Another area of obvious importance is cancer, where appropriate medicinal treatments are severely lacking.

The incidence of cancer in children and adolescents is about 10 to 15 cases per 100,000, representing approximately 1,800 new cases each year in France and 12,000 annually in Europe. Malignancies diagnosed before the age of 19 years represent 1% of all human cancers. More than 60 different malignancies occur in children consisting of solid tumours (70%) and leukaemias (30%). The most frequent malignancies are leukaemias (30%), brain tumours (20%), lymphomas (11%), neuroblastomas (8%) and sarcomas of the bones (5%) and soft tissues (7%). The prevalence of each of these malignancies is below 1 per 2,000 in the European Union¹⁵.

Major progress has been made in the treatment of paediatric malignancies in the last 30 years. In favourable settings, current treatment protocols (chemotherapy, surgery and radiotherapy) yield cure rates exceeding 70%. However, certain metastatic tumours (neuroblastoma, sarcomas of the bones and soft tissues) and brain tumours (medulloblastoma, ependymoma and glial tumours) are associated with cure rates below 50%. New treatments are clearly required.

Thus, it is believed nearly one in three children cannot be cured by current treatments. Approximately 3,800 children and adolescents (under 19 years) die of cancer each year in Europe. The development of new therapies is one of the major objectives in paediatric oncology in the coming decade, with the aim of both increasing the cure rate and reducing toxicity.

Conclusions on the current status of paediatric therapies

The current status of paediatric therapies clearly shows that many drugs used in paediatric fields are either not licensed for use in children or are prescribed outside the terms of their product license.

Appropriate information on medicinal products used in children is therefore an important priority for paediatric medicines: children have characteristics which vary with their age, and a medicinal product intended for children requires appropriate pharmaceutical presentation to ensure easy and safe administration. For this purpose, taking into account the fact that children are not “small adults” in terms of reaction to medicines, clinical trials are needed. The highest scientific and ethical standards have to be applied to this clinical research, the aim of which is to provide useful information (risk/benefit ratio, dosages, etc.) to drug agencies and thereafter to prescribers.

Paediatric clinical development is therefore essential so that children may benefit from an effective treatment appropriate for their weight and age. This will not only improve efficacy but also reduce the risk of adverse drug reactions.

Barriers to paediatric research

The public view on performing clinical research in children has undergone a shift in recent years. The high potential benefits of new drugs in saving and improving quality of life are today clearly perceived, and it is recognised that withholding new and effective treatments from children for unnecessarily long periods is unethical.

It is also now recognised that the present situation forces the medical community to prescribe in an uncontrolled, unlicensed fashion, when they have to use medicinal products for which data in children or in the respective age groups are not available. This has ethical implications as well.

It is not disputed that clinical studies are required, and the need to protect children from unnecessary trials is more and more weighed against the need to perform necessary clinical trials in children. This will be done under strict official rules set up at the EU level.

In its December 2000 Resolution, the Health Council noted that: *“As regards medical treatment, children have characteristics which vary with their age and physical development and which mean that in most cases they cannot be treated like adults; in particular, a medicinal product administered to a child has specific characteristics in terms of pharmacokinetics, effectiveness and undesirable effects; furthermore, a medicinal product intended for children requires appropriate pharmaceutical presentation, to ensure appropriate and effective administration”.*

Making available medicinal products assessed specifically for paediatric use with acceptable formulation and dosage involves potentially difficult pharmaceutical

Children are not small adults

On the one hand, there are medical needs specific to children that require the development of medicines for these populations in particular. On the other hand, medicines developed for adults should be adapted before they are administered to paediatric populations.

Children go through different stages of development, which involve variations in body weight, surface area, physiology, kidney function as well as liver, cognitive or immune function. This influences the impact medicines may have on them (e.g., pharmacokinetic/pharmacodynamic considerations). Clinical trials in these specific populations are therefore required to assess the effectiveness and safety of medicines.



development and clinical trials. Research in children presents scientific, technical, practical and ethical challenges of importance¹⁶, which involve further risk-taking by the sponsor of the studies.

Problems specific to paediatric research are detailed in the Guideline on Clinical Investigation of Medicinal Products in the Paediatric Population (ICH Topic E11)¹⁷ - a number of these are summarised below:



Timing of paediatric development

The determination of the most appropriate time to initiate a paediatric development program for a medicinal product is difficult. It will depend on many factors, including the type of medicinal product, the nature of the disease, safety considerations, and the efficacy and safety of alternative treatments in children. Paediatric trials may not be appropriate during the licensing stage for medicines that are going to be used particularly in adults, and for which paediatric activity is still to be determined. This also raises the issue of conduct of clinical trials on children before real knowledge of the safety profile of medicine has been obtained.

Paediatric formulations

Specific paediatric formulations must be developed to allow accurate dosing, facilitate consumption and enhance patient compliance. As provided in the ICH Guideline¹⁸:

- "For oral administration, different types of formulations, flavors and colors may be more acceptable in one region than another. Several formulations such as liquids, suspensions, and chewable tablets, may be needed or desirable for paediatric patients of different ages. Different drug concentrations in these various formulations may also be needed." Development of these products can be difficult and there is a high risk of failure (for example: the inability to conceal the bitter taste of a product, the lack of stability of a reconstituted solution, etc.). Acceptable formulations should be accompanied by an adequate and safe delivery system, which can be difficult to manufacture.
- "For injectable formulations, appropriate drug concentrations should be developed to allow accurate and safe administration of the dose. For medicinal products supplied as single-use vials, consideration should be given to dose-appropriate single-dose packaging."
- "The toxicity of some excipients may vary across paediatric age groups and between paediatric and adult populations, e.g., benzyl alcohol is toxic in the preterm newborn. Depending on the active substance and excipients, appropriate use of the medicinal product in the new-born may require a new formulation or appropriate information about dilution of an existing formulation. [...]"

Pharmacokinetic studies

Pharmacokinetic studies are often difficult to conduct in children. In this population, they are generally conducted in patients with the disease. This may lead to higher inter-subject variability than studies in healthy volunteers. The consent for participation may be more difficult to obtain. Pharmacokinetic studies in children also require taking into account various practical considerations.

For instance, the volume of blood withdrawn should be minimised, which poses technical and procedural challenges. The ICH Guidelines list various approaches to be adopted for this purpose:

- Use of sensitive assays for parent drugs and metabolites to decrease the volume of blood required per sample;
- Use of laboratories experienced in handling small volumes of blood;
- Collection of samples for pharmacokinetic analysis should coincide with routine, clinical blood sampling whenever possible;
- Use of indwelling catheters (with topical anaesthesia to place IV catheters); and
- Use of population pharmacokinetics to minimise the number of samples obtained for each patient.

Furthermore, the development of non- or minimally invasive methods (saliva, urine...) for pharmacokinetic assessments is required.

Efficacy and safety studies

- As underlined in the ICH Guidelines, where efficacy studies are needed, it may be necessary to develop, validate and employ different endpoints for specific age and developmental subgroups. Measurements of subjective symptoms, such as pain, require different assessment instruments for patients of different ages.
- The adverse event profile may differ in paediatric patients: some adverse events and drug interactions that occur in paediatric patients may not be identified in adult studies. In addition, the dynamic process of growth and development may not manifest an adverse event (in the short run), until a later stage of growth and maturation. Long-term follow-up studies may be required (e.g., in cancer where more than 2 out of 3 children with cancer survive disease-free and become active adults) to determine possible effects on skeletal, behavioural, cognitive, sexual maturation and development, and to detect cardiotoxicity, renal sequelae, or secondary malignancies.

Age classification in paediatric populations

In the majority of paediatric developments, clinical trials are performed in various age ranges.¹⁹

Pre-term new-born infants

The study of medicinal products for this population presents special challenges because of the unique spectrum of diseases afflicting this population, the rapid development and differences in their body functions (even within this subset group), the unique response to treatment, and the requirements for forms of medications that can be safely administered given their especially small size.

Term new-born infants (0 to 27 days)

This population is more mature than the pre-term, but volumes of distribution of medicinal products may be different than those in older paediatric patients, and the blood-brain barrier is not fully mature. Furthermore, oral absorption may be less predictable than in older paediatric patients and hepatic and renal clearance mechanisms are immature and rapidly changing.

Infants and toddlers (28 days to 23 months)

This is a period of rapid mental, physical and immune development. Elimination of drugs from the body may exceed that in adults. Since development does not occur at the same rate in all children, there may be considerable variability in response to medication even in children of the same age.

Children (2 to 11 years)

Given the large variation and variability in development in this age group, recruitment of patients must ensure adequate representation across all ages in this category. The onset of puberty, which is highly variable, heralds a time of accelerated growth and marked changes which may alter response to medications and the doses required.



Adolescents (12 to 16/18 years)

In this period of sexual maturation, medicinal products may interfere with the actions of sex hormones and impede development. It is also a period of rapid growth and continued neurocognitive development. As this group of young adults strives to balance independence with responsibility, their willingness to take medically required therapies becomes a particular problem. This creates a challenge in improving or developing medications to improve the possibility that they will be taken as directed.

Ethical issues

The paediatric population represents a vulnerable subgroup. The obligation to act in the child's best interest requires that he/she be protected from potential risks of research – which poses the dilemma of weighing these risks against those involved in prescribing medicines that have not been studied in the relevant paediatric population. Clinical trials in children must be scientifically and ethically valid, while ensuring a favourable risk v. benefit ratio, and complying with appropriate standards including those specifically designed for paediatric populations.²⁰

The role of the ethics committee is critical to the protection of study participants. If it is to protect children who participate in trials, the committee should have the necessary expertise in paediatrics.



A paediatric subject is not legally able to provide informed consent. Fully informed consent must be obtained from the parents/legal guardians, and, depending on the age of the child, the child must also give assent or consent (commensurate with their understanding and experience). The communication of sufficient, adequate and comprehensible information to the parents and eventually to the child in need of treatment raises concerns as to the actual ability of these individuals to give informed consent. This can be particularly problematical when it is requested in an emergency situation, or at the time when diagnosis of a disease with poor prognosis (such as cancer) is made known.

Minimising risk and distress

Every effort must be made to minimise risk to children involved in clinical studies. For this purpose, investigators conducting the study should be specifically trained and properly experienced in the treatment of paediatric patients. This should also aim to minimise the discomfort and distress for the individual subject.

Protocols and investigations should be designed for the paediatric population – and not simply re-worked from adult protocols. According to the ICH Guidelines, practical aspects that should be considered for this purpose include the conduct of studies in familiar settings and adapted physical environment, with furniture, play equipment, activities, and food appropriate for the age group.

Financial considerations

Costs are very variable, depending on the nature of the disease, the extent of the programme needed and the duration of the trials. On a per-patient basis, and as a general rule, direct costs are similar to those for trials in adult patients. However, indirect costs can be much higher due to the difficulties in performing the necessary studies, as outlined above. Paediatric pharmaceutical formulations, specifically developed for



various age categories, are expensive. However, rather than costs, it is the greater risk and difficulty of conducting research in children that constitutes the primary barrier.

Conclusions on barriers to paediatric research

The development of medicinal products specifically adapted to children, with appropriate dosage and formulation, will require in many cases the conduct of extensive, specific studies. Nevertheless these are necessary in numerous cases where safety and efficacy in children cannot be extrapolated from data obtained through trials conducted in adult populations. This is more so considering the need to determine adequate dosages in different age groups (to avoid under- or over-treatment). As often voiced by the scientific community: "children are not small adults."

Despite practical difficulties faced by sponsors and researchers in conducting studies in children (e.g., stemming from the small number of children with a certain disease or the recruitment of these patients), they are nevertheless key to the elaboration and improvement of therapies for children.

Challenges for all including the pharmaceutical industry

The European research-based pharmaceutical industry already plays an active role in improving pharmaceutical treatment of children of all ages.

However, the obstacles listed above, together with general constraints due to resource management, as well as risks involved for the sponsor because of considerations such as liability that may stem from the conduct of studies in children, discourage the conduct of research programmes in paediatric indications²¹.

It is time to ensure a substantial European contribution to the worldwide process of providing better medicines for children. For this purpose, science and research conducted by both academia and industry in Europe should be appropriately strengthened and stimulated.

The need for more effective measures in the European Union was already highlighted in the European Health Council's Resolution on Paediatric Medicinal Products dating from December 2000, and was re-iterated in December 2003²².

It was reiterated as well in the framework of the G-10 High Level Group on Innovation and Provision of Medicines, which recommended in May 2002 that Commission and Member States "put in place an effective policy in terms of incentives to research and support the development and marketing of orphan and paediatric medicines"²³.

The European Commission has worked on a legislative proposal on medicinal products for paediatric use (see box).

The research-based pharmaceutical industry generally welcomes the introduction of Community measures that would take into account the specificities and structure of the European market and pharmaceutical regulatory system. However, there is great concern as to the ensuing delays in the concretisation of these initiatives. As time passes, opportunities to develop new medicines are missed, and children are deprived of more adapted therapies.

The main features of the Commission proposal include:

- the creation of a dedicated scientific and regulatory body at the European Agency;
- creation of "paediatric investigation plans";
- implementation of specific requirements and regulatory processes;
- introduction of incentive models in the form of intellectual property (IP) protection when the paediatric data pertain to medicinal products which are still under such protection;
- specific marketing authorisations for older medicines for which a paediatric use is developed;
- creation of specific funding mechanisms for paediatric investigation concerning older medicines;
- setting up of a pan-European network of paediatricians with specific competence in clinical trials in children;
- means to communicate information on paediatric development and use, including the creation of a database on paediatric trials.

Conclusion

Better medicines for children in Europe, to improve their health and general welfare, is to be a common, high priority goal for all.

Government officials, the scientific community, health professionals, patients and their parents, and industry, are aware of the current problems, and everyone agrees that a solution is urgently needed.

The research-based industry strongly believes that measures must be implemented which will provide the necessary stimulus to R&D activities for paediatrics in Europe.

- 1 "It is estimated that over 50% of [medicines used in children], particularly in specialised medicine, have never actually been studied for use in children." European Commission, Enterprise Directorate-General, "Consultation Document on Paediatrics 'Better Medicines for Children - Proposed regulatory actions on Paediatric medicinal products'" (Brussels, 28 February 2002).
- 2 "Off label use" refers to medicinal products used for an indication, age group, dosage, route of administration outside the terms of the product's marketing authorisation. Sutcliffe, A G, "Testing new pharmaceutical products in children – A positive step, but ethical concerns remain", *BMJ* 2003; 326: 64-65.
- 3 Turner S, Gill A, Nunn AJ, Hewitt B, Choonara I. "Use of "off-label" and unlicensed drugs in paediatric intensive care unit." - *Lancet* 1996; 347: 549-550; Turner S, Nunn AJ, Choonara I. "Unlicensed drug use in children in the UK" - *Paediatric Perinat Drug Ther* 1997; 1: 52-55; Turner S, Longworth A, Nunn AJ, Hewitt B, Choonara I. "Unlicensed and off label drug use in paediatric wards: prospective study" - *BMJ* 1998; 316: 343-345; Turner S, Nunn AJ, Fielding K, Choonara I. "Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study" - *Acta Paediatrica* 1999; 88: 965-968; Conroy S, McIntyre J, Choonara I. "Unlicensed and off label drug use in the neonate." - *Arch Dis Child Fetal Neonatal Ed* 1999; 80: F142-F145; Wilton LV, Pearce G, Mann RD "The use of newly marketed drugs in children and adolescents prescribed in general practice." - *Pharmacoepidemiology and drug safety*, 1999; 8: 537-545; Chalumeau M, Treluyer JM, Salanave B, Assathiany R, Cheron G et al. "Off label and unlicensed drug use among French office based paediatricians" - *Arch Dis Child* 2000; 85: 502-505; Martin R et al "Unlicensed and off label drug use for paediatrics patients" - *Letter to the British Medical Journal*, July 1998, 317,204.
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- 7 Mc Intyre J, Conroy S, Avery A, Corns H, Choonara I. "Unlicensed and off label prescribing of drugs in general practice" - *Arch Dis Child* 2000; 83: 498-501; Wilton LV, Pearce G, Mann RD "The use of newly marketed drugs in children and adolescents prescribed in general practice." - *Pharmacoepidemiology and drug safety*, 1999; 8: 537-545.
- 8 Turner S, Gill A, Nunn AJ, Hewitt B, Choonara I. "Use of "off-label" and unlicensed drugs in paediatric intensive care unit." - *Lancet* 1996; 347: 549-550; Turner S, Nunn AJ, Choonara I. "Unlicensed drug use in children in the UK" - *Paediatric Perinat Drug Ther* 1997; 1: 52-55; Turner S, Longworth A, Nunn AJ, Hewitt B, Choonara I. "Unlicensed and off label drug use in paediatric wards: prospective study" - *BMJ* 1998; 316: 343-345; Turner S, Nunn AJ, Fielding K, Choonara I. "Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study" - *Acta Paediatrica* 1999; 88: 965-968.
- 9 The Pediatric Exclusivity Provision - January 2001 Status Report to Congress - Department of Health and Human Services - US Food and Drug Administration: 14.
- 10 Mc Intyre J, Conroy S, Avery A, Corns H, Choonara I. "Unlicensed and off label prescribing of drugs in general practice" - *Arch Dis Child* 2000; 83: 498-501.
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- 13 Mc Intyre J, Conroy S, Avery A, Corns H, Choonara I. "Unlicensed and off label prescribing of drugs in general practice" - *Arch Dis Child* 2000; 83: 498-501.
- 14 Turner S, Gill A, Nunn AJ, Hewitt B, Choonara I. "Use of "off-label" and unlicensed drugs in paediatric intensive care unit." - *Lancet* 1996; 347: 549-550; Turner S, Nunn AJ, Choonara I. "Unlicensed drug use in children in the UK" - *Paediatric Perinat Drug Ther* 1997; 1: 52-55; Turner S, Longworth A, Nunn AJ, Hewitt B, Choonara I. "Unlicensed and off label drug use in paediatric wards: prospective study" - *BMJ* 1998; 316: 343-345; Turner S, Nunn AJ, Fielding K, Choonara I. "Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study" - *Acta Paediatrica* 1999; 88: 965-968.
- 15 Vassal G. – data on file – June 2001.
- 16 As reiterated in Sutcliffe, A G, "Testing new pharmaceutical products in children – A positive step, but ethical concerns remain", *BMJ* 2003; 326: 64-65.
- 17 The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use – Harmonised Tripartite Guideline on Clinical Investigation of Medicinal Products in the Paediatric Population (ICH Topic E11) is available at: <http://www.ich.org>
- 18 Guideline on Clinical Investigation of Medicinal Products in the Paediatric Population (ICH Topic E11), p. 3.
- 19 To note, age classification in Europe differs from the one to which is generally referred in the United States.
- 20 Sample of rules on ethical and methodological aspects of clinical trials in children defined by EU institutions: Note for Guidance on the Clinical Investigation of Medicinal Products in Children (CPMP/ICH/2711/99 – adopted July 2000); European Parliament and Council Directive 2001/20/EC on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use, Official Journal of the European Communities, L121, p. 34, 01/05/2000.
- 21 This stems from the results of a study designed to evaluate the number and characteristics of medicines approved for children in Europe by the EMEA through the centralised procedure from January 1995 to September 2001 – reported in: Ceci A, Felisi M, Catapano M et al, "Medicines for children licensed by the European Agency for the Evaluation of Medicinal Products", *Eur J Clin Pharmacol* (2002) 58: 495-500. According to the study (excerpts): The median percentage of drugs authorised for children in this timeframe is 35% of the total commercially available drugs. Only 16 medicines have been approved for children under 2 years of age (11%), ten of these being vaccines. 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. The study concludes that under the centralised procedure, several active substances have been licensed for children, and that consequently serious and life-threatening disease as AIDS and diabetes are now treatable. However, the number of drugs devoted to children remains low (especially in important ATC classes as oncology and neurology). At the same time, few medicinal products are specifically studied in children.
- 22 The Council invited the Commission "to make appropriate proposals as soon as possible in the form of incentives, regulatory measures or other supporting measures in respect of clinical research and development, taking account of the ethical aspects of clinical trials in children, to ensure that new medicinal products for children and medicinal products already on the market are fully adapted to the specific needs of that population group, and taking into account also the internationally acknowledged standards for the protection of minors with regard to medical scientific research." European Union – Health Council Resolution on Paediatric Medicinal Products, December 14, 2000, Official Journal of the European Communities, C-17, p. 1 (19/01/2001); in 2003, the Council called on the Commission "to come forward with a set of incentives, regulatory measures and other supporting measures to encourage the development and marketing of paediatric medicines." European Union – Health Council Resolution on Pharmaceuticals and Public Health: Challenges – Focusing on the Patients, December 2, 2003, Official Journal of the European Union, C-20, p.2 (24/01/2004).
- 23 G-10 Medicines - High Level Group on Innovation and Provision of Medicines – Recommendations for Action (Report), Recommendation IX "Incentives for Research". Available from: <http://dg3.eudra.org/F3/g10/docs/G10-Medicines.pdf>

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