



Testing medicines for children in Europe

Paediatric clinical trials are still underrepresented in Europe despite new regulations. This is in marked contrast to what happened in the US after similar laws were introduced. The European CRO Federation (EUCROF) considers the situation in Europe in the light of new data from selected European countries

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Gaining sufficient knowledge about the use of medicines in children and adolescents is a global health priority. Children and adolescents represent about 25% of the European population¹ and more than half of the medicines used in this population have not been formally tested and evaluated. Rather, medicines unlicensed for paediatric use are given off-label to children.

This widespread practice has been of increasing concern over the past few years since this experience is not often translated into clinical practice guidelines and represents a danger to the child in terms of underdosing (lack of efficacy), or overdosing (toxicity).² The lack of appropriate pharmaceutical formulations to allow the effective and compliant administration of many medicines in children is a further issue.

Moreover, the conduct of formal paediatric research is still underrepresented in the European Union (EU).³ A recent survey that evaluated the number of clinical studies and marketing authorisations for 2003 and 2004 in Germany found a total of 44 clinical studies and 28 marketing authorisations⁴ for the most important paediatric diseases.

The Clinical Trials Directive (2001/20/EC) was expected to simplify clinical trials and therefore stimulate clinical research. However, its implementation has not yet had a positive effect on the number of studies being conducted in paediatrics. Germany is one country where this has been evaluated.⁴ However, the situation described for Germany may not be representative of the situation in all European countries. Furthermore,

the conclusions of the survey are limited because an important number of data were lost due to not returned questionnaires. The need for more studies to obtain paediatric information on medicines used in children was a matter of consensus on a global basis.² Based on this, it is clear there is a need for a legal obligation on pharmaceutical companies to also develop their medicines for the paediatric population, if appropriate, and thus to perform clinical trials in that population.²

Situation in the US

Regulations have already been implemented in the US. In 1997 the Food and Drug Modernization Act (FDAMA) came into force⁵ encouraging the evaluation of drugs used in children. In 2003 the Paediatric Research Equity Act⁶ gave the legal right to the Food and Drug Administration (FDA) to ask for drug research in children. The FDA has taken a carrot-and-stick approach to encourage studies in children. The 'carrot' is the Pediatric Exclusivity Provision of the FDA Modernization Act that became law under the Best Pharmaceuticals for Children Act (BPCA) in 2002. BPCA gives drug manufacturers a voluntary incentive to acquire an additional six months of marketing exclusivity — the ability to sell their drug without competition from generic drugs — if they conduct paediatric studies on drugs that the FDA determines may be useful to children.

The 'stick' has been the pediatric rule, finalised in 1998 and basically passed as the Pediatric Research Equity Act (PREA) in 2003.⁶ PREA authorises the FDA to require manufacturers of new drug and biologic products to conduct paediatric studies in certain circumstances.

Together these two acts have encouraged the development of important new information for drugs used in children. As of February 20, 2009, labelling changes have been made to more than 260 products that were studied in children under BPCA or PREA. Of the more than 170 drugs studied just under the exclusivity incentive programme within the BPCA, 159 have new paediatric labeling information including:

- 45 drugs with new or enhanced paediatric safety data that hadn't been known before
- 27 drugs with new dosing or dosing changes

- 50 drugs with information stating they were not found to be effective in children

As a result, the complexity of studies in children has increased, with efficacy and safety studies representing 40% of all paediatric studies conducted in 2006 compared with 25% in 2000.⁷ Paediatric study costs rose substantially from 2000 as complexity grew.

Situation in Europe

In December 2006, the European regulator, the EMEA, released new paediatric medicines regulation. This requires all new medicines or existing drugs covered by a Supplementary Protection Certificate where a variation to the licence is requested, to be studied in children (if applicable) in order to generate data that will be mentioned in the label.⁸ A waiver to conduct studies in all or some paediatric populations can be given if the medication is expected to be not safe or effective in children, if the indication does not occur in children, or if the product does not represent a significant therapeutic benefit over existing medications.

A paediatric investigation plan (PIP) has to be submitted at an early stage of clinical development⁹ and agreed with the Paediatric Committee (PDCO), which was established within the EMEA to examine the need for medicines in paediatrics and gives opinions about the PIPs. In return for generating this data, and provided the product is subsequently registered in all member states, patent protection will be extended by six months.

Moreover, in order to stimulate paediatric research for authorised products no longer covered by intellectual property rights, a new Paediatric Use Marketing Authorisation (PUMA) was implemented under the regulation. This provides specific market protection for medicinal products developed for exclusive use in the paediatric population.

European CRO Federation overview

In order to get a concise overview on the current status of paediatric research in Europe, the European Contract Research Organisation (CRO) Federation EUCROF conducted a series of surveys shortly after implementation of the Regulation.

Before going into the results of the surveys it is worth giving an overview of EUCROF, which was founded in October 2005 as an umbrella organisation of national CRO associations. It represents the interests of CROs in the EU in close communication with regulatory bodies, the pharmaceutical and biotechnological industry, as well as with the medical and affiliated research community.

EUCROF has its headquarters in the Netherlands and operating offices in Paris. It is a non-profit organisation that is funded by its subscribing members, the national CRO associations. It aims to promote clinical research by improving the knowledge, competence/expertise and skills of clinical researchers in the EU by networking initiatives and information exchange in congresses

Table 1: Members of EUCROF

Country	National association	Number of CROs
Czech Republic	ACRO-CZ	22
France	AFCROS	50
Germany	BVMA	25
Italy	AICRO	15
The Netherlands	ACRON	31
Spain	AECIC	23
United Kingdom	CCRA	30
Total:		196

Table 2: Number of paediatric clinical trials published on www.clinicaltrials.gov for the period 2005, 2006 and 2007

Sponsor	Number of Trials	Active Trials	European Countries	US	Others	Phase I	Phase II	Phase III
Pharmaceutical companies	52	65%	37%	56%	39%	17%	29%	50%
Universities	96	60%	9%	84%	28%	40%	27%	26%

Multiple responses were possible, therefore totals exceeded 100%

and meetings. EUCROF also develops training and educational programmes for clinical research, helps its members to implement EUCROF's recommendations in national programmes and supports the global distribution of information on clinical research to health professionals.

EUCROF is headed by an executive board that consists of four people, appointed for a two-year-period. The current president of the executive board is Antoine Cournot of France. EUCROF has initiated five working groups, among them the paediatric working group (PWG).

Surveys of the paediatric working group

The PWG aims to increase knowledge about the methodology of clinical trials in children, to train investigators in European countries, to improve the relationship between CROs, the pharmaceutical industry and the competent authorities in Europe and North America, and to alert society in general to the need to develop paediatric information for medicines through conducting clinical studies.

In that respect and for the purposes of its surveys, the PWG has identified sources of information on clinical studies in children in order to gain more complete information about the paediatric situation in selected European countries. These sources include paediatric networks and organisations or working groups in European countries as well as scientific events covering paediatrics

A paediatric network can be understood as a virtual structure defined by a formal agreement between individuals, organisations or structures sharing and collaborating towards the same objectives, goals and quality standards.¹⁰

Data were collected by means of a standardised questionnaire per country. The questionnaire covered the respondents' awareness of the number of clinical studies (general and paediatric) in the respective territory, the number of paediatric working groups and investigator networks and the number of paediatric conferences.

All available data bases and sources of information were used. The information was collected by members of the EUCROF PWG between February 2008 and August 2008. EUCROF was successful in collecting information about 15 countries, which comprised 13 EU countries plus Russia and Ukraine (see Table 4).

After a preliminary analysis, EUCROF came to the conclusion that the results of the initial survey may be limited by various factors because some

sources of information, networks or conferences may not have been detected. The different size of the participating countries (in 2007, Spain had about 45 million inhabitants while Estonia had about 1.3 million) also has to be taken into consideration, while the organisation grade of the networks and the extent of their activities may vary. In Germany and other EU countries, paediatric oncology trials have been conducted for decades by large national competence networks with investigators from universities, hospitals, specialised practices and scientific institutes. The conferences may also vary with regard to their size and content.

The quantitative information obtained from the different countries showed that clinical paediatric trials are increasing and CROs are performing 30-40% of the trials. But it also made clear to EUCROF that additional data should be collected to avoid the bias already mentioned. After further research on the web, EUCROF found some other trends, which are highlighted in Tables 2 and 3, showing respectively where paediatric trials are conducted, and on which age ranges.

US is favoured location

The data show the preferred location of paediatric trials was the US. As was to be expected, universities were more involved in early research (Phase I trials) while pharmaceutical companies conducted more Phase III studies and trials involving younger children up to nine years old. Table 4 summarises the number of clinical trials in the period 2005, 2006 and 2007, the number of paediatric trials in the same years, the number of paediatric working groups, the number of investigator networks, and the number of paediatric conferences in different European countries.

These data show that paediatric trials and paediatric working groups are probably underrepresented in most European countries. In some countries (Austria, Estonia, Germany, Lithuania, Spain and Ukraine), more than 10% of the clinical trials conducted are paediatric studies. However, others (Bulgaria, Denmark, Italy, Latvia and Russia) have very few paediatric trials (less than 10% of all clinical trials). The same can be observed for the paediatric working groups. While Austria, Bulgaria, Germany, Italy, Spain and the UK have a relevant number of paediatric working groups, only a few working groups are present in Denmark, Estonia, Ireland, Latvia, Lithuania, Portugal, Russia and the Ukraine. Spain and Germany had

Table 3: Number of clinical trials published on www.clinicaltrials.gov per age range

Sponsor	Patient age			
	< 3 years	< 8 - 9 years	< 17 - 18 years	< 25 years
Pharmaceutical companies	54%	70%	33%	17%
Universities	68%	70%	54%	23%

Multiple responses were possible, therefore totals exceeded 100%

the most paediatric conferences, with 25 and ten respectively.

Discussion of results

Pharmaceutical companies may prefer to conduct paediatric studies with experienced sites and investigators, so European paediatric trials may be concentrated in a few European countries. On the other hand, the data also show that countries with potential for conducting more paediatric trials may exist.

It is noteworthy that the EU implemented the paediatric rules as a regulation, ie, as directly effective law, which is not modified by national authorities. This ensures consistent requirements within the entire EU, which may make it more attractive to conduct studies anywhere in the EU. In contrast, the Clinical Trials Directive was implemented by the national authorities with some country-specific modifications, which led to delays in coming into operation in several EU countries and also to some inconsistencies in requirements across countries. The more rigid approach of the Paediatric Regulation may therefore contribute to a better and earlier effect with a rapid increase in paediatric clinical trials.

Nevertheless, the number of paediatric trials appears to be very low and demonstrates the need for intensified paediatric research. It is expected that the EU Paediatric Regulation will stimulate paediatric

research and that the number of clinical studies in the various European territories will increase as has occurred in the US. Due to the fact that time is needed for the approval and implementation of PIPs, it will take some time before the effect of the Regulation will be reflected in a real increase of paediatric clinical trials.

New EUCROF initiative

Therefore, and in order to collect additional and more comprehensive information about paediatric medicines in Europe, EUCROF has commenced a further initiative by disseminating a new questionnaire, which covers the more practical aspects of conducting clinical studies in children. It aims to gather statistics about paediatric research from the CRO, pharmaceutical companies and medical ethical committees. In so doing, hurdles to the conduct of paediatric research can be identified. The Regulation aims to contribute to the improvement of safety information of paediatric drugs, to the increase of knowledge about paediatric drug doses, and to the improvement of therapeutic options in a special patient population. EUCROF aims to identify trends in this research activity. The second survey has meanwhile been completed; an in-depth analysis is ongoing and will be presented to the EMEA and other bodies with a vested interest in clinical research in children.




Table 4: Paediatric activities in selected European countries

Country	Number of clinical trials between 2005 and 2007	Number of paediatric trials between 2005 and 2007	Number of paediatric working groups	Number of investigator networks	Number of paediatric conferences
Austria	1840	225	14	1	8
Bulgaria	650	45	22	5	6
Czech Republic*	692	10	1	11	7****
Denmark	807	66	5	6	4
Estonia	200	27	1	1	4
Germany	5700	850	50	4	10
Ireland	355	n.a.	2	n.a.	5
Italy**	2183	33	26	1	5
Latvia	160	13	1	2	3
Lithuania	196	25	2	3	2
Portugal ¹¹	147***	n.a.	2	1	5
Spain	179	23	84	14	25
UK ¹²	2660	547	13	15	5
Russia	1518	72	2	0	4
Ukraine	298	36	1	n.a.	2

*2006 and 2007 ***2007 only ****2008 data
 ** Data from national trials database. The respondent CRO only conducted one paediatric study in this period.

Conclusion

In conclusion, the initial EUCROF survey has demonstrated the need for intensified paediatric research. The survey showed that the proportion of clinical studies as well as the organization grade of paediatric researches still varies remarkably between European countries. EUCROF will do further investigations to provide more insight into the current status of paediatric research. 

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