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Contents

EDITORIAL

Medicines for Children in Europe at the Beginning of the New Millennium

The rational use of medicines in children is an objective that is being addressed more and more often in European initiatives. Several significant events have occurred since the end of the year 2000. These are, in chronological order:

- The European Council approved a resolution that will allow the harmonisation of, and provide the incentive to, perform clinical research on medicines for the paediatric population in the single member states and in the entire European Union. This important step follows on from an initiative by the European Medicines Evaluation Agency[1], a specific document on paediatric research aimed at the pharmaceutical industry and regulatory authorities[2], and a recent directive by the European Parliament and Council concerning good clinical practice (GCP), with a few statements specific to children[3];

- The first meeting of the Drug Agencies of the Member States was held, with the aim to create a formal network for the planning of regulatory activities and the monitoring of drug use and safety in the paediatric population;

- The creation of a meta-register of controlled clinical trials, with particular emphasis placed on the paediatric aspect.

We hope to inform readers of the issues relevant to their professional activities and to lead them towards active participation in this sector.

Paediatric Medicinal Products – European Resolution

During the assembly held on December 14, 2000, the European Community's Health Council discussed and approved the proposal by the Presidency regarding a resolution concerning medicines used in children. The proposal highlighted the limited availability of adequate drugs for use in children and suggested a decisive intervention at the European level. More specifically, it asked the commission to make proposals based on incentives, regulatory interventions or other strategies that will favour clinical research and the development of new medicinal products for children as well as the adaptation to paediatric needs of drugs already present on the market.

The approved resolution (Document 301Y0119(01)) reads as follows:

"THE COUNCIL OF THE EUROPEAN UNION,

1. RECALLS that a high level of health protection is to be ensured in the definition and implementation of all Community policies and activities and that Community action, complementing national policies, is to be directed towards improving public health, preventing human illness and diseases and obviating sources of danger to human health;

2. NOTES that nearly 20% of the Community population, i.e. seventy-five million people, is under the age of 16;

3. NOTES that, as regards their treatment, children have characteristics which vary with their age 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 easy and safe administration;

4. NOTES that a large number of the medicinal products administered to children have not been assessed specifically for paediatric use and may therefore not meet the criteria of quality, safety and effectiveness required in the case of adults;

5. OBSERVES that the prescription of medicinal products to children is therefore very often not

covered by the marketing authorisation and that, taking into account the shortage of paediatric pharmacovigilance data, safety of use in this population group cannot therefore be documented by monitoring studies after marketing;

6. RECOGNISES that making paediatric medicinal products available involves difficulties of pharmaceutical development and of clinical development. The necessary research and development costs are not amortised because of the small number of children affected by each disorder in each age bracket;

7. CONSIDERS that the development of paediatric medicinal products and clinical trials involving children may give rise to specific ethical concerns and that children must benefit from special protection;

8. CONSIDERS that all Member States face this problem and that a European approach offers advantages from the epidemiological, public health and economic points of view;

9. ACCORDINGLY INVITES 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 on 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."

Health Council meeting of 14.12.2000

Agencies Seminar on Medicinal Products for Children

The need for drugs developed specifically for paediatric use has been established, as it has been shown that many drugs have not been formally tested in children[4]. Following the USA's example, a few initiatives regarding drug regulation are being taken in Europe.

One initiative is the proposal to establish a *Paediatric Network* formed by all European National Health Agencies to: harmonise drug information for children; determine which and how many drugs lack optimal formulations for their use in children to be rational; and create a list of drugs present on the market that need further trials for use in the paediatric population.

These were the issues addressed in Paris (December 2000) in a meeting organised by the French Agency (Afssaps, Agence française de sécurité sanitaire des produits de santé). Representatives of the European Commission, the Food and Drug Administration, other European scientific societies such as the European Network for Drug Investigation in Children[5] and the European Society for Clinical Pharmacy, many national health agencies and the pharmaceutical industry, all participated. All participants were enthusiastic about the way forward. Collaboration on the part of paediatricians, pharmacists, parents and 'organisations belonging to the pharmaceutical field' will be essential both at national and European level.

In such a context, the involvement, not only of paediatricians, but also hospital pharmacists and pharmacists working in pharmaceutical services and clinical pharmacies, could be a useful contribution to the issue, and, more importantly, could assist in achieving a more rational use of drugs for children[6].

An International *meta*Register of Controlled Trials (mRCT)

When well-designed and correctly carried out, controlled clinical trials – ideally randomised – (RCTs) are a fundamental tool for verifying a health-related hypothesis. They are an objective evaluation of the relationship between research and clinical observation[7]. RCTs occupy a modest space among the various interventions in the health-care field. This limited space is significant, however, if the importance of the effects of their outcomes are taken into consideration (e.g. the efficacy of a treatment, the effectiveness of an intervention).

Despite this importance (priority) for a population's health and the ever increasing technological, world-wide transfer of knowledge, it is surprisingly difficult to access the results of RCTs and even to find out which RCTs are currently running and which are planned for the future. Once completed, not all RCTs are published (especially those with negative results), even in minor journals, or else are published only as abstracts or in an inadequate manner, etc[8].

How many RCTs are actually being carried out? How many of these are truly necessary or are unique and not duplicates? When dealing with paediatrics, one cannot avoid thinking about

what happened, and continues to happen, regarding the treatment of acute otitis media, to mention just one paediatric example[9]. All this does not relate directly to research methodology, but concerns research ethics. Avoiding trial duplication, or the sub-optimal planning or execution of studies, or even the interruption or 'fading into nothingness' of clinical studies, not only avoids unnecessary costs, but also avoids the useless (when not harmful) enrolment of patients (and their expectations) into trials[10].

Avoiding all possible futility related to carrying out trials is a strong concern for researchers, evidence-based methodologists and even certain international health agencies. It is not so, however, for the pharmaceutical industry[11]. A few initiatives have been undertaken along these lines: a register of ongoing trials with public access, created by the American NIH and located at the web site www.ClinicalTrials.gov and a British *meta*Register (mRCT) created by *Current Controlled Trials* with the supervision of the *Lancet* and the *BMJ*, allowing access to 15 international clinical trials registers for a total of 6500 trials (www.controlled-trials.com).

At the Royal College of Medicine in London (January, 2001) all these issues, as well as possible future strategies, were discussed. Representatives of the NIH, the American Veterans' Program, the International Cochrane Center, the Medical Research Council, a few European health agencies and international research centres, as well as a representative of the pharmaceutical industry, participated in this event organised by *Current Controlled Trials*.

Children's health and the special needs regarding therapies and research that make children an underprivileged population with respect to medicine and the evaluation of the benefit–risk profile of interventions, were some of the issues addressed[12,13]. A first draft of a register of clinical trials in paediatrics in Italy, that should become active before the end of the year and possibly be extended to the European level in the future, was also presented[14]. This is an important, unique initiative, even in light of the recent ministerial changes concerning trials outside the hospital setting, that will also involve family paediatricians. In order to succeed, this initiative will require the contribution and participation of paediatricians as well as of hospital pharmacists and general pharmacists, not only in a national context, but also in a European one.

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