Pharmacological Research 64 (2011) 169–175

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

The development of medicines for children

Part of a series on Pediatric Pharmacology, guest edited by Gianvincenzo Zuccotti, Emilio Clementi, and Massimo Molteni

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ARTICLE INFO

Article history:
Received 26 January 2011
Accepted 27 January 2011

Keywords:
Child
Drug approval
Clinical trial
Europe
Drug legislation

ABSTRACT

The lack of availability of appropriate medicines for children is an extensive and well known problem. As a consequence off label or unlicensed administration of medicinal products in every day paediatric practice is frequent.

A variety of obstacles hinder the development of paediatric indications for drugs primarily intended for the adult market. The barriers to proper research on children's drug development include several complex factors, such as the limited commercial interest, lack of suitable infrastructure and competence for conducting paediatric clinical trials, difficulties in trial design, ethical worries and many others.

Medicinal products used to treat children should be subjected to ethical research of high quality and be explicitly authorised for use in children as it happens in adults. Conducting adequate clinical trials in children is challenging and demanding. Identification of paediatric medical needs, extrapolation from adult data, modelling and simulation, specific clinical trial methodology are important features in the development of drugs intended for children.

Market forces alone have proven insufficient to stimulate adequate research aimed at specific authorisation of medicinal products for the paediatric population, and for that reason, following the US experience, the European Paediatric Regulation has been amended in January 2007 by the European Commission. The objective of the Paediatric Regulation is to improve the development of high quality and ethically researched medicines for children aged 0 to 17 years, to facilitate the availability of information on the use of medicines for children, without subjecting children to unnecessary trials, or delaying the authorisation of medicines for use in adults.

The impact of the Paediatric Regulation reflects in an increase in the number of paediatric studies to be performed, even if a significant number of these studies have not started yet.

The objective of this review is to describe the main regulatory and scientific features which play a role in the complex issue of paediatric drug development.

Contents

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doi:10.1016/j.phrs.2011.01.016

1. Background

Drug development is a very complex process, that revolves around a balancing of requirements of several stakeholders, including those of science, pharmaceutical industry, regulatory authorities, ethics, politics and, not least, patients. The main goal is to guarantee that high quality medicines with a favourable benefit/risk profile are made available to the individuals who need them.

1.1. The European regulatory environment

Prior to marketing a medicinal product in the European Union (EU), a marketing authorisation (product licence) must be obtained. This means that the products have to undergo specific "regulatory" studies to ensure its quality, safety and efficacy for use in the target population. These studies are often not published in peer-reviewed journals, as this is not a requirement for registration; nevertheless, the quality of these regulatory studies is very often higher than that of published studies, as the limitations of the peer review system are well known [1,2]. Furthermore, regulatory agencies that decide on marketing authorisation have the possibility to conduct inspections of trial sites and original data, something usually impossible for academic journals and peer reviewers.

In the EU, there are four types of marketing authorisation:

1. National marketing authorisations: issued by the competent authorities of individual EU member states; the medicinal product may be put on the market in all Member States that have granted an authorisation for it.
2. Community marketing authorisation: this is a single authorisation that allows the medicinal product to be put on the market in all Member States. It is granted by the European Commission, following a positive opinion from the European Medicines Agency (EMA).
3. Mutual Recognition Procedure: that means that European countries may approve the decision made about a medicinal product by another European country.
4. Decentralised procedure: used for products that have not yet received authorisation in an European country.

In both cases, the conditions of use are laid down in the summary of product characteristics (prescribing information for health professionals), the labelling, and the package leaflet (for users/patients).

A summary review of the regulatory processes for the authorisation of medicinal products in the EU is contained in the guide for small and medium enterprises published by the EMA [3].

1.2. Few data are available on the safety and efficacy of medicines in children

Until now, a lack of information on the paediatric uses of most medicinal products has continued to affect the paediatric population (in the European Union, this refers to children from birth to less than 18 years old).

Even if children represent more than 20% of the European population, with about 100 million people aged less than 18 years, children have often been denied proper access to new medications, or they are treated with medications which have not been subjected to a scientific assessment in the same age groups. The lack of specific labelling recommendations for the paediatric population is a long-standing worldwide problem: it is estimated that 50–75% of medicines used in children have not been studied adequately in the paediatric population [4–7], and many have not been tested at all [8]. When special paediatric populations are considered, the situation is even worse: more than 80% of medicines for children with cancer and about 90% of prescriptions for neonates are for products which have not been licensed for that use [9–11].

Often, an assumption that safety and efficacy will be the same as in adults is implicitly accepted, but this is very often not based on any evidence. Using medicines that have not been approved by the appropriate regulatory authorities in the specific age groups makes children, particularly the younger ones, constant participants in uncontrolled N-of-1 trials.

1.3. Harm is associated with off-label use in children

The consequence of the above is frequent off-label administration of medicinal products in everyday paediatric practice. Off-label use (which means outside the terms of the marketing authorisation) may be supported by limited evidence in the form of published reports in the scientific literature, not followed by explicit regulatory approval. However, in some cases no evidence at all is available to support the use in a given indication/condition. This last occurrence, which may put children at increased risk, is considered tantamount to unauthorised clinical experimentation by some national legislations, with possible serious consequences to the practitioners (in addition to the risk for the patients).