European regulatory framework on the use and development of pharmaceuticals and radiopharmaceuticals for pediatrics

Marguérite M. Mensonides-Harsema PhD[1]
Andreas Otte M.D[2,3]

1. D-22587 Hamburg/Germany
2. Faculty of Electrical Engineering and Information Technology, University of Applied Sciences, D-77652 Offenburg
3. Department of Economics, Insurance and Health Care Management, WHL Graduate School of Economics, D-77933 Lahr/Germany

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Correspondence address:
Professor Andreas Otte MD, Professor of Biomedical Engineering, Faculty of Electrical Engineering and Information Technology, University of Applied Sciences, Badstr. 24, D-77652 Offenburg/Germany
E-mail: andreas.otte@fh-offenburg.de
www.fh-offenburg.de

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Abstract

A survey in 2000 revealed that only about 30% of the prescriptions in the European pediatric population were on the basis of evidence-based medicine (EbM). Less for radiopharmaceuticals and principally for diagnostics, radiologists throughout Europe are referred to the pediatric guidelines of the European Association of Nuclear Medicine (EANM), as none of the frequently used tracers have been evaluated in clinical trials in the different pediatric subgroups. Following a resolution to address the lack of EbM in children, the European Commission published the Pediatric Regulation EC 1901/2006 and its amendment EC 1902/2006, effective from 2007. This regulation foresees the development of evidence-based medicine in the pediatric population. This is effected through a set of principles like the mandatory pediatric investigation plan (PIP) to be included with the market authorization application (MAA), and the pediatric use market authorization (PUMA) for off-patent pharmaceuticals, and to a very small part radiopharmaceuticals with funding possibilities for pediatric-specific research through the 7th Framework Programme (7FP) of the European Union.

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Introduction

The purpose of this article is to describe the Pediatric Regulation EC 1901/2006, its elements, investigation plans, marketing authorization and also its implications for future radioactive and non-radioactive drug development for the pediatric population. Furthermore, we shall describe some of the effects established by the pediatric regulation in nuclear medicine research and development and the impact on the global advancement of pediatric evidence-based medicine through extensive collaborations between the European Medicines Agency and the Food and Drug Administration.

In the early 2000's a study revealed that although about 20% of all the prescriptions throughout Europe were for children, only 7% of the clinical trials performed had been in children [1-4]. In the United States of America, in response to legislation, pediatric studies conducted between 1998 and 2002 had led to 34 labels containing new pediatric information for established medicines. In 12 cases these new labels included important new dosing, pharmacokinetic or safety information that had an impact on the safe and effective use of these medicines in the pediatric population [5, 6]. In addition, there are numerous practical challenges in administration of 'adult' formulations. For example, children might have difficulties swallowing tablets. Or, more significantly, physicians or pharmacists may make calculation errors when using adult formulations and weight adjustments to obtain pediatric dosages, leading to either underdosing (ineffective treatments), or worse, overdosing (adverse effects due to treatments). The European Medicines Agency has published several reflection papers on the safety, suitable formulations and important role of drug metabolism and pharmacokinetics property (DMPK) studies in the pediatric population [7-9]. For the use of radiodiagnostics and radiopharmaceuticals in the pediatric population, the possibility to rely on evidence-based medicine is even more limited. To date, there are about 70 registered radiopharmaceuticals – this number varies slightly between the different European countries and the United States of America –, of which about 10% are used as radiotherapeutics [10, 11]. In Germany the Federal Office for Radiation Protection (Bundesamt fur Strahlenschutz) is the competent authority for approval of clinical research with pharmaceuticals conjugated with a radionuclide, the already limited number of pediatric clinical trials has been restricted mostly to the studying of non-radioactive pharmaceuticals. Although there may be ethical concerns about conducting clinical trials in the pediatric population, this has to be balanced by the ethical concerns about giving (radio) pharmaceuticals to a population in which they have not been properly evaluated for their safety and therapeutic efficacy [12, 13]. A descriptive example of the situation is the re-

stricted development and use of radio-immune treatment (RIT) in oncology in the pediatric population. Cancer is a rare disease in children. Pediatric malignancies account for about 1% of all cancers in humans, with 15.000 children being diagnosed with cancer in Europe each year. The life expectancy and possibilities for treatment of children with cancer has dramatically improved over the last decades. This has mainly been achieved through investigator initiated trials [14]. For example, in low-grade non-Hodgkin's lymphoma, the mode of action of radiopharmaceuticals is as follows: a monoclonal antibody conjugated to a β-emitting radioisotope binds to a specific antigen, for example the CD20 expressed by follicular B-cells in non-Hodgkin's lymphoma (NHL) and deliver radiation not only to the tumor cells that bind the antibody, but also to neighboring tumor cells that are either inaccessible to the antibody or that express this particular antigen insufficiently (cross-fire effect). The two most widely studied and still recently approved radio-immune treatments for the treatment of non-Hodgkin's lymphoma of the current generation are ^{90}Y-labelled ibritumomab tiuxetan (Zevalin®, Bayer Schering, Germany) and ^{131}I-labelled tositumomab (Bexxar®, Corixa and GlaxoSmithKline, United States of America), both demonstrating a high level of activity in patients whose CD20+ follicular/low-grade or transformed non-Hodgkin's lymphoma has failed to respond to other treatment or who have relapsed after an initial remission phase. So far, one prospective phase I investigator-initiated trial has been completed and published, studying the use of ^{90}Y-ibritumomab tiuxetan in a small high-risk group of children and adolescents with progressive/refractory high-grade B-cell non-Hodgkin's lymphoma, showing it to be safe and well-tolerated. However, an announced phase II investigator initiated pediatric clinical trial remains to be initiated [15]. ^{131}I-labelled tositumomab is only approved in the United States, and received orphan designation by the European Commission in 2003 for the treatment of follicular lymphoma. Pharmaceuticals that receive a 'designated orphan medicinal product' status are still considered investigational products and have not (yet) been granted market authorization in the member states of the European Union. The legislative background for the designation of orphan medicinal product status is the EC Orphan Disease Regulation 141/2000. Other, still investigational radio-immune treatments studied in B-cell non-Hodgkin's lymphoma include LL2 (the non-humanized murine antibody of epratuzumab that is directed against CD22) conjugated to either an ^{131}I or ^{90}Y radionuclide, anti-HLA-DR (Lym-1) monoclonal antibody conjugated to either the ^{90}Y or ^{67}Cu radionuclide (directed against CD22), rituximab conjugated to either the ^{211}At or ^{186}Re radionuclide (directed against CD20), and the monoclonal antibody B4 conjugated to the ^{90}Y radionuclide (directed against CD19) [16].

The objectives of the Pediatric Regulation EC 1901/2006 are to: Increase research quality, promote the development and authorization of pharmaceuticals appropriate for the pediatric populations, and improve related information [17-19].

A pediatric use market authorization can be granted, offering 10 years of market exclusivity to the applicant for the use of the off-patent drug in the pediatric population upon the presentation of additional information to the European Medicines Agency. In addition, the 7th European Framework Programme (2007-2013) has launched specific calls for proposals to support pediatric studies on old drugs that are of interest for the treatment of children but that are unlikely to be funded by large pharmaceutical companies [20].

Development of the Regulatory Framework

The main features of the Pediatric Regulation EC 1901/2006 - with its aim to improve the pharmaceuticals available for the pediatric population are [21, 22]: a) The Pediatric Investigation Plan (PIP), b) the Pediatric Use Marketing Authorisation (PUMA), c) the Pediatric Committee (PDCO).

The pediatric committee (PDCO)

The pediatric committee consists of pediatricians, physicians, pharmacists and a few pre-clinical professionals. These 'competent authorities' are nominated by the Committee for Medicinal Products for Human Use, the European Union member states, the members of the European Free Trade Association and by patients' and health care professionals' interest groups and meets 13 times per year [23].

The pediatric committee is not responsible for market authorization applications of medicinal products for pediatric use. This responsibility remains fully within the remit of the Committee for Medicinal Products for Human Use, in accordance with Regulation EC No 726/2004 [24]. Figure 1 illustrates the involvement of the pediatric committee and the process of the pediatric investigation plan procedure over time. Prior

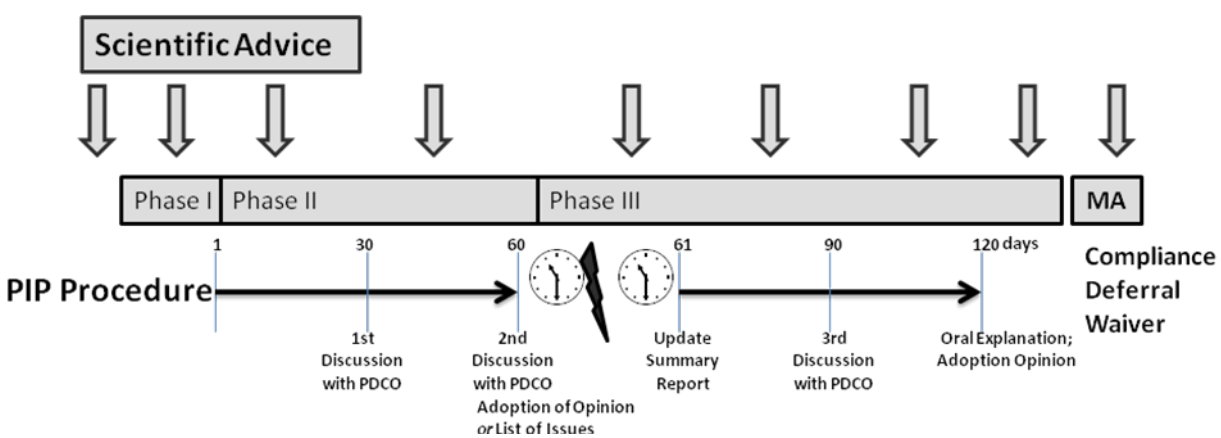

Figure 1. Timelines for consultations with pediatric committee and the pediatric investigation plan procedure.

to obtaining market authorization, a final compliance check with the agreed pediatric investigation plan will be carried out. Waivers will be granted if the pharmaceutical product is unlikely to benefit children, if clinical studies are impractical or impossible in specified pediatric populations, or if there is already existing evidence of ineffective and/or unsafe use of the pharmaceutical product in children. Waivers are either disease or formulation specific. The pediatric investigation plan is a 120-day procedure with a clock-stop phase of circa 3 months, during which the applicant can amend the pediatric investigation plan according to the requests and proposals of the pediatric committee.

Pediatric investigation plan (PIP)

The European Medicines Agency uses the following definition of the pediatric investigation plan: 'a research and development program aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorized to treat the pediatric (sub-) population'. In principle the pediatric investigation plan should cover among other prerequisites all subsets of the pediatric population, existing and new indications and (new) routes of administrations as well as appropriate formulations about pediatric age, proof concept for in vivo or in vitro studies, pharmacokinetics and toxicity studies [25]. The pediatric investigation plan application documents are set-up in 5 sections (A-E) plus appendices (F) [26, 27]. Normally, when the pediatric investigation plan procedure leads to the authorization of specific pediatric indications for a patent-protected, marketed drug, the market authorization holder is obliged to place the product on the market together with the pediatric information, within two years of the date of approval of the indication.

The pediatric use marketing authorization (PUMA)

The European Medicines Agency uses the following definition of the pediatric use marketing authorization is 'a marketing authorization granted in respect of a medicinal product for human use which is not protected by an supplementary protection certificate under Regulation (EEC) No 1768/92 or by a patent which qualifies for the granting of the supplementary protection certificate, covering exclusively therapeutic indications which are relevant for use in the pediatric population, or subsets thereof, including the appropriate strength, pharmaceutical form or route of administration for that product' [28]. Substitution practices of off-patent trademark medicinal products for generic products or products that show similar therapeutic effects are a well-established practice throughout the different European member states.

EC 7th Framework Programme and increased evidence-based medicine in pediatric treatments

Medicinal products are widely used outside the terms of the market authorization and summary of product characteristics (labeling) to treat children. Thanks to the Pediatric Regulation EC 1901/2006, the development of specific (older) medicinal products for children, including those no longer covered by a patent or supplementary protection certificate, has become more attractive. These studies are needed because medicines do not behave in children's bodies as they do in adults, and specific age appropriate formulations are needed to allow safe and effective administration of accurate doses. Thanks to the 7th Framework Programme, funding, to cover the costs of the development of off-patent drugs for children has become available to individuals, academics, research centers and networks, and small and medium enterprises, including generic pharmaceutical companies. Accepted collaborations need to consist of three independent participants from three different European Union member states or associated countries. Project proposals from these collaborations meaning to close identified gaps in the pediatric Evidence-based Medicine or aiming for a pediatric use marketing authorization for an European Medicines Agency -identified pediatric priority indication may receive up to a maximum of € 6 million per project. The total budget for the high level theme 'health' of the 7th Framework Programme is set at € 6.1 billion to be spent over seven years (2007-2013). In order to ensure that funds are directed into research of medicinal products with the highest need in the pediatric population, the pediatric committee has adopted a priority list of treatments and off-patent pharmaceuticals for which studies are required [29].

Impacts of Pediatric Regulation EC 1901/2006: status quo

Every year, over 6 million patients benefit from a nuclear medicine procedure in Europe, 95% of which are diagnostic and 5% therapeutic [30]. In Europe, radiopharmaceuticals are considered a special group of diagnostics and medicines. Therefore, their preparation and use are regulated by a number of European Union directives, regulations and rules that have been adopted by member states. The rate of adoption of directives varies between countries and each member state may introduce changes, provided the general scope and limits of each directive are maintained [31, 32]. From a practical point of view the following four situations may arise: a) a licensed radiopharmaceutical product is used either within or outside its authorized indication, b) a radiopharmaceuticals product that has established clinical use is prepared in accordance with approved regulations and meets approved quality requirements or c) a new radiopharmaceutical drug or tracer agents outside the previous categories is used/prepared [31].

One of the outcomes of the Pediatric Regulation and the 7th Framework Programme is the project peddose.net, titled 'Dosimetry and health effects of diagnostic applications of radiopharmaceuticals with particular emphasis on the use in children and adolescents' [30]. The project is a collaboration between the Germany, Belgium and France, coordinated by the European Institute for Biomedical Imaging. Research (EIBIR) and supported by Dosimetry Committee of the European Association for Nuclear Medicine [33-37]. The project will receive financial support (€ 500.000) from the 7th Framework Programme and is supposed to present its final report in the fall of 2011.

Pediatric investigation plans, waivers and deferrals. Further results of the Pediatric Regulation so far are the refusal of a product specific waiver for all subsets of the pediatric population from birth to less than 18 years of age for rubidium-82, a radionuclide generator that it's sponsor (Advanced Accelerator Applications, France) intends to develop as a diagnostic for the visualization of myocardial perfusion for diagnostic purposes [38]. On 18 May 2009, the European Medicines Agency came back with a negative decision based on the opinion of the pediatric committee that the waiver request did not provide evidence to support the statements

that rubidium-82 was likely to be ineffective or unsafe in the pediatric population nor that the disease or condition for which the specific radiodiagnostic is intended occurs only in adult populations nor that the specific medicinal product could not represent a significant therapeutic benefit over existing diagnostic techniques for pediatric patients. Another pediatric investigation plan procedure concerns rituximab (Mabthera®, Roche Products Ltd, Switzerland), a monoclonal antibody that targets the CD20 antigen, which is present on the surface of all B-lymphocytes. When rituximab attaches to the antigen, causes cell death. Rituximab is currently licensed for the treatment of lymphoma and chronic lymphocytic leukemia, since it destroys the cancerous B-lymphocytes and in rheumatoid arthritis, where the destruction of the B-lymphocytes helps to reduce inflammation. The original authorization date of rituximab by the European Medicines Agency is 2 June 1998. The new indications filed by Roche Products Ltd are autoimmune arthritis and diffuse large B-cell lymphoma. For autoimmune arthritis a waiver has been granted to all subsets of the pediatric population from birth to less than 18 years of age on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments. However, for diffuse large B-cell lymphoma, the waiver only applies to children from birth to less than 6 months of age as clinical studies are deemed to be not feasible [39]. The results of clinical trial could open the door for further investigation of radio labeled rituximab, ^{90}Y-ibritumomab tiuxetan and ^{131}I- tositumomab in the pediatric population, as these CD20 antigen specific monoclonal antibodies also target B-lymphocytes, combining this mode of action with the destructive radiation of the radionuclides they are conjugated with [40-42]. The routine use of radioimmune treatment, however, still poses some challenges, like the need for adequate budgets and reimbursement systems and a specific radio-immune treatment diagnosis-related group (DRG) code throughout most of the European Union member states [42]. In other words, the general availability of these innovative, hopefully superior treatments in the pediatric population is possibly still a few years ahead of us.

European Medicines Agency and the Food and Drug Administration

Together with the EC Orphan Disease Regulation 141/2000, the Pediatric Regulation EC 1901/2006 forms a strong legislative basis for the development of more appropriate and safe medicinal products specific for the treatment of rare diseases in children. This is important as the palette of radiopharmaceutical products with evidence-based clinical safety and efficacy in the pediatric population is disappointingly limited. Both administrations build their regulations on the principles declared in the International Conference of Helsinki E-11 guidelines: 'pediatric patients should be given medications that have been appropriately evaluated for their use in such populations, the development of product information in these patients should be timely, the well-being of pediatric patients that participate in a clinical trial should not be compromised and the responsibility for the health of pediatric patients is one that is shared among regulatory authorities, health professionals, the pharmaceutical industry and society as a whole' [43, 44].

Important differences in legislation in the United States of America and European Union exist [45, 46] but they are not the issue of this article.

Over the past years, the two regulatory authorities have started an intensive exchange of scientific and ethical information on pediatric development programs including also radiopharmaceuticals that are either ongoing or have been completed in either/both European Union and the United States of America, with the ultimate goal of avoiding exposing children to unnecessary clinical trials, while, at the same time, optimizing the global pediatric developments. These intensive discussions are of detrimental importance for the pediatric population and for the chance of success of the actual development of evidence-based medicine for children. The anticipation that in some years the safety-, quality- and efficacy-assurance of pharmaceutical products used in children will mirror the confidence existing today for these same products when used in adults is hopefully justified.

In conclusion, with the introduction of the EC Pediatric Regulations 1901/2006, the number of submitted pediatric investigation plans to the European Medicines Agency and the incentive for the pharmaceutical industry to develop their new drugs, including radiopharmaceuticals and their true innovative ones, for the pediatric population as well, has increased significantly. The fact that, so far, only one of 413 pediatric investigation plans [47] concerns the development of a radiopharmaceutical is, however, a reason for (continued) concern.

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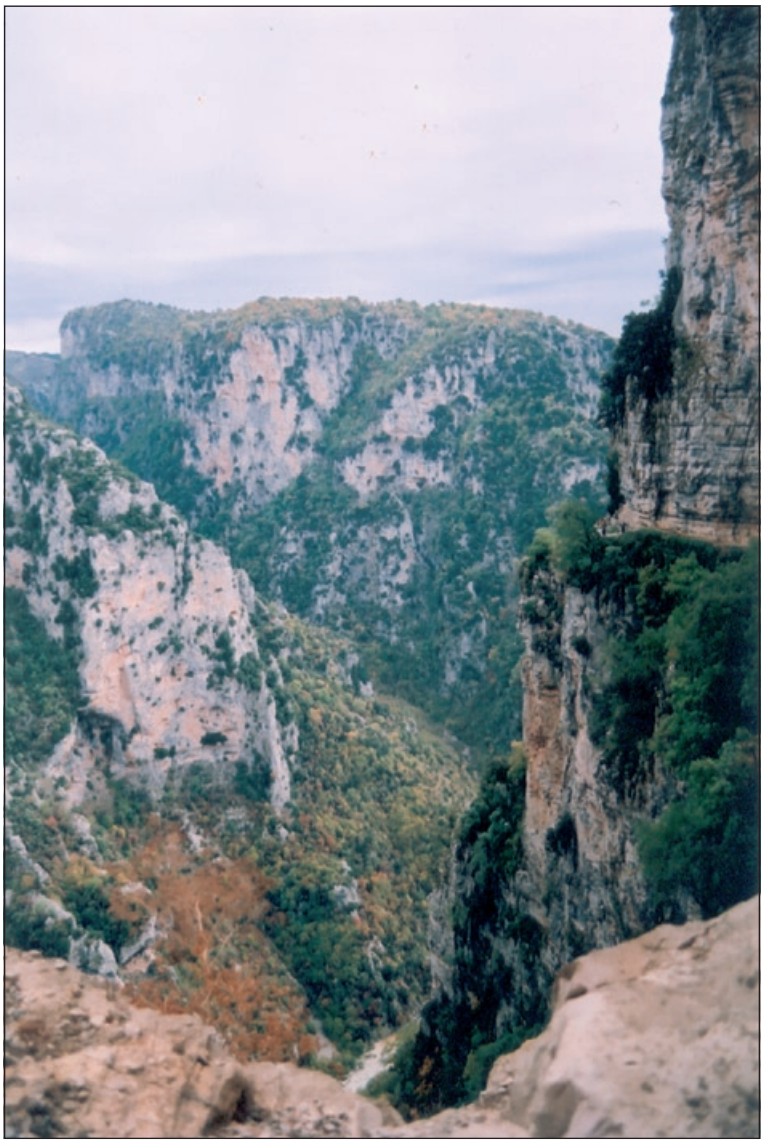

Prof. Ioannis Dokmetzioglou. *Vikos Canyon in Epirus, Greece - about 1000m deep*