*Review Article*

# European Union Pediatric Legislation Jeopardizes Worldwide, Timely Future Advances in the Care of Children With Cancer

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## ABSTRACT

**Background:** Diagnosis of childhood cancer is no longer an automatic death sentence, but it has not lost all of its horror. Drugs, surgery, radiation, and clinical trials have advanced our capacity to handle these cancers, but pediatric cancers still face challenges. Pediatric pharmaceutical legislation was introduced in the United States in 1997 and has triggered many clinical trials that have helped us better understand what drugs do to a child's body and vice versa. Following the US precedence, the European Union introduced its own legislation. The US legislation was designed to generate additional pediatric data and balances between mandatory requirements and voluntary incentives. The EU legislation was deigned to mandate full registration of all new drugs for children whenever there is any potential pediatric use.

**Objective:** The purpose of this article is to discuss unintended negative consequences of the legislation of the European Medicines Agency (EMA).

**Methods:** We analyzed the effects of the EU pediatric legislation with respect to the history of the emergence of modern drugs, pediatric clinical pharmacology, and the development of drugs for pediatric malignancies.

**Results:** No new drug can be registered in the European Union without a detailed pediatric investigation plan (PIP) approved by the EMA's Pediatric Committee (PDCO). This has moved the discussion of the pediatric aspects of drug development to an earlier stage and has increased public awareness. It also has brought industry and pediatric oncologists closer together. However, in a review of >100 PDCO PIP decisions in childhood cancer, we found a lack of balance between the legitimate desire to include children in drug development and the common sense needed in the complex worlds of drug development and pediatric oncology. Many decisions appeared to have been based on both exaggerated assumptions about the frequency of childhood malignancies and the feasibility of the clinical trials proposed.

**Conclusions:** Pharmaceutical companies are being forced into long-term commitments to clinical trials before efficacy in adults has been demonstrated. Pediatric clinical oncology trials are being driven by regulatory "tunnel vision" and not by therapeutic benevolence, epidemiologic data, or feasibility. As a result, children with cancer are being monopolized for PDCO-triggered, often unfeasible trials that are not always in their best interests and seldom produce useful therapies. Because clinical trials are global, this affects children with cancer worldwide. Until now, carefully worded concerns about these negative consequences have been published in specialty journals. It is time to start a broader debate on how to move forward. (*Clin Ther*. 2014;36:163–177)


**Key words:** childhood cancer treatments, clinical trial regulations, European Union, oncologic drug development, pediatric oncology, pediatric trials.

## PEDIATRIC ONCOLOGY, NEW DRUGS, MODERN LABELS, AND OFF-LABEL USE OF DRUGS IN CHILDREN

Cancer is quite different in children than in adults. Adult cancer is relatively frequent, whereas cancer in

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children is relatively rare, but both share 1 characteristic: they can kill. One hundred years ago, little could be done in either adults or children; but then, fewer adults reached the age at which most adult cancers develop. Adult cancer treatment evolved with the 3 pillars of surgery, radiation, and drug treatment. With some delay, these principles were also applied to children, with surprising results. Pritchard-Jones et al[1] wrote that "childhood cancer is one of the success stories in the history of cancer treatment, with 5-year survival of 80% or more now being achieved in high income countries."

Modern pharmaceutical treatment evolved with the scientific revolution and with modern industry. Powerful drugs were synthesized, but it took 2 catastrophes—the sulfanilamide elixir in 1936 and thalidomide in 1961—to open the path to modern drug regulation in which the safety and efficacy of any drug must be proven in clinical and other trials.[2] This signaled the advent of the modern label. Instead of allowing the manufacturer to claim whatever it would like to claim, modern labels reflect the outcomes of clinical and other trials. This also led to the pharmaceutical term *off-label use*—use of a drug in a therapeutic area or age group for which the drug is not registered. From 1961 on, most drugs in children were prescribed off-label.[3]

Cytotoxic and other agents have been developed and approved for adults since the 1950s. Learning how to use them in children took pediatric oncologists additional decades. They collaborated very early in international clinical trials.[1] In the face of the potential death of a child, most parents agree to include the child in one or several clinical trials, so that participation in a clinical trial is today regarded as a "gold standard" in the treatment of cancer in children. Most treatment schemes for children with cancer, however, are still off-label and probably will never be registered. The regulatory authorities did not play a major role in the revolution of pediatric oncology, but they also did not interfere.[4] However, they played a key role in properly testing and licensing adult anticancer drugs.

Most drugs today are developed by pharmaceutical companies, even if in some instances the original scientific discovery on which they are based comes from academia. Drug development has become a complex process from early discovery through preclinical and clinical development to marketing. This development is very expensive.[5,6] The cost of a new drug is today estimated at over US $1 billion. The chemical industry became the pharmaceutical industry and is today the health care industry or life sciences industry. The availability of powerful drugs predominantly for adults and their off-label use in children had several consequences, among them the evolution of pediatric clinical pharmacology as a subspecialty of clinical pharmacology.[7,8]

In the 1960s, pediatric disclaimers were introduced by drug manufacturers, largely to lessen the chances of being sued, emphasizing that the respective drug had not been specifically investigated in children. Because of this, Shirkey in 1968 referred to children as "therapeutic orphans" because children were excluded from the pharmaceutical drug-development progress.[3]

## GLOBALIZATION OF PEDIATRIC CLINICAL RESEARCH

Pediatric cancer is so rare that clinical trials have always required a larger recruitment area than just 1 hospital, 1 state, or even larger regions. In the United States, in 2009, 4 collaborative research groups that each conducted such trials merged voluntarily into the Children's Oncology Group (COG).[9] Pediatric clinical trials are performed today increasingly on a global basis,[10,11] as are adult trials. There are several reasons for this, including the lack of availability of patients and research center costs, as well as a need for an appropriate physical and technical framework and a spirit that welcomes rather than discourages clinical research.

A discouraging example of the latter is provided by the EU clinical trials directive of 2001.[12] Introduced to establish an EU-wide framework for clinical research, the bureaucratic obstacles it introduced led to a one-fourth reduction in the number of EU clinical trial applications and to an increase in costs.[13] The 27 EU national bureaucracies found 27 different ways to interpret the directive, so in 2012, the EU commission published a proposal to replace it with a new regulation.[13] A regulation in the European Union is hierarchically higher than a directive: it is immediately applicable in all EU member states, without the need for adaption into 28 national legislations (now 28 because Croatia joined the European Union in 2013).

## CLINICAL PHARMACOLOGY AND PEDIATRIC PHARMACEUTICAL LEGISLATION

In the United States, pediatric pharmaceutical legislation was first introduced as part of the US Food and Drug Administration's (FDA) Modernization Act and