



## The Vision of Better Medicines for Children and the Role of Regulatory Authorities

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Pharmaceutical pediatric legislation was introduced in the USA in 1997 as the FDA Modernisation Act (FDAMA) [1] and in 2006 in the EU as the EU Paediatric Regulation [2]. In 2007 the WHO kicked off campaign titled “Make Medicines Child Size”. In the British Medical Journal the WHO campaign is characterized as follows: “An initiative from the World Health Organization has been launched to make drugs as simply and safely available to children as they are to adults [3].

Is there anybody on this planet who would raise his voice against a slogan like “better medicines for children”? Probably not. When we organized first conferences in Europe following the introduction of the EU pediatric regulation, we tried to find a respected academic speaker to take the part of criticizing the legislation in a controversial debate. For several years, we couldn't find anybody. Why? Nobody wanted to be the bad guy who is *against* children's health. When things are not controversial at all, often there are aspects nobody wants to speak about. The EU pediatric legislation has a stronger emphasis on mandatory requirements than the US legislation. While the FDA can enforce pediatric development only in the same indication as in adults, in the EU the EMA uses a construct called ‘condition’ and expands the scope of pediatric research beyond the adult indication. Furthermore, rare diseases, vaccines, and even drugs for diseases that exist only or predominantly in children are not exempt from having to submit a pediatric investigation plan (PIP) before a market authorisation application can be requested. Are separate efficacy studies in adolescent patients feasible? Do they medically make sense? Or should simply the adult dose be used? What about ultra-rare diseases? Another reason why nobody is against something is when a concept sounds just noble. Usually things remain noble as long as they are pure theory. As soon as they get in touch with reality, things become more complex.

The US pediatric legislation was re-authorized in 2012 as FDASIA without the need to re-authorize it again, i.e. as long as it is not changed, it will remain valid [4]. The EU pediatric legislation is now in force since 2007, and today, in 2014, we have collected a lot of experience with this legislation. Regarding the consequences for research in pediatric oncology, the EU pediatric legislation and the ensuing activities of the pediatric committee (PDCO) have a few times been criticized by academic researchers [5,6] and now a first time more in depth by a pediatric consultant [7]. Metastasized melanoma in adolescent is so rare that maybe 1 to 3 patients are newly diagnosed per year per EU member state. Is it feasible to force industry to investigate drug efficacy separately in adolescents if the advanced disease is so rare? There are now 5 melanoma PIPs listed on the EMA website [8-12], and probably none of the studies that companies had to commit themselves to will ever be finalized simply because the patients don't exist. On the other side, the UK Cancer Research Institute has published a press release asking the EMA pediatric committee (PDCO) to force even more pediatric research out of pharmaceutical industry [13]. So, the controversy has just started.

Pediatric oncology evolved since the 1950's when increasingly cytotoxic agents became available for the treatment of adult cancer. It took the clinical research community decades longer to find out the accurate doses and combinations for the treatment of child cancer. Since the 1960ies the survival rate of children with adult lymphatic leukemia increased by 10% with each decade that passed, and the survival rate is

today around 90%. A huge success story. But in this success story the regulatory authorities did not play a key role. All children with cancer were treated off-label [14,15]. Today we see how the EMA wants to play a new key role in further improving the treatment of child cancer. But are they able to do so? The agency's job is to regulate drug licensing, not to get operationally involved and direct drug development.

Drug development is complex, controversial, and expensive [16-18]. The critical debate about the role of regulatory authorities in providing better medicines for children is gaining momentum. FDA and EMA work closely together. But there are also fundamental differences, and specifically in the desired push to consider children more in drug development the EMA wants to have a leading role. There is no doubt about the EMA's good intentions. But good intentions can have disastrous consequences. The inquisition in Europe wanted «only» to save people's souls against devilish thoughts, but at the end the priests acted like devils themselves. But that is another story. We will certainly see a hot debate about better medicines for children in the near and mid-term future.

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