

## Comment on: Mumme M, et al. Tissue engineering for paediatric patients. Swiss Med Wkly. 2019.149.w20032

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We agree with Mumme et al. that tissue engineering in young patients represents many unmet medical needs and has immense promise [1]. However, they do not explain the discrepancy between the visionary aims of the European Union (EU) paediatric legislation and its meagre results. Herein, we address three key issues and draw conclusions.

1. “Children are not small adults” is correct for newborns, less correct for pre-pubertal children whose bodies are slowly maturing, and inaccurate for adolescents, who are bodily mature but legally still “children”. The regulatory term “children” blurs physiological and legal characteristics of young persons [2, 3].
2. The characterisation of children as “therapeutic orphans” emerged in 1968 in the USA, led to the first paediatric law in 1997 that rewarded voluntary paediatric studies and was later complemented by another law that allowed FDA-mandated paediatric studies. The EU paediatric law was passed in 2007. The “therapeutic orphans” concept was triggered by toxicities in newborns treated with antibiotics in the 1950s [4], as well as the increased FDA authority as of 1962 in the wake of the thalidomide disaster [2, 3, 5]. Subsequently, companies inserted paediatric warnings into labels as protection against exaggerated damage lawsuits typical of the US judicial system [2, 3, 5]. The US paediatric laws reflect(ed) a coalition of the American Academy of Pediatrics (AAP) and paediatric learned societies, the FDA, and industry that profited from patent extensions [2, 3, 5]. The FDA defined “children” as <17 years old. But only neonates are as immature as claimed for all “children” [6]. In our opinion, the FDA-rewarded/mandated “paediatric” studies did not benefit all young patients. Most were/are guided by regulatory logic and tunnel vision, not by therapeutic intention. For example, the FDA rewarded studies of single cytotoxics in “children” (up to 21 years old!) with cancer [5] when paediatric oncology already routinely combined many cytotoxics [5, 7]. Regulatory logic demands separate efficacy studies in “children”,

resulting in “paediatric” placebo-controlled trials in multiple sclerosis [8], depression [9], allergic rhinitis [10] and more diseases. The EU expanded the FDA approach, defined “children” as <18 years of age and demands “paediatric” studies in areas even beyond the FDA’s reach, including drugs for rare diseases, vaccines, allergen products and autologous biotissues.

3. For EU approval, companies must commit to “paediatric investigation plans” (PIPs). Mumme et al. outline that only two autologous biotissue products are European Medicines Agency (EMA)-approved, including Spherex (spheroids of human autologous matrix-associated chondrocytes) for autologous chondrocyte implantation (ACI) of the knee. The Spherex PIP demands a “paediatric” study in patients between closure of the epiphyses and 17 years of age [11], i.e., in bodily mature but legally still underage patients. Four more ACI PIPs demand comparable inclusion criteria [12–15]. Apart from separate “paediatric” proof of efficacy, two PIPs demand randomised comparison of ACI vs microfracture, a less effective procedure to treat damaged knee cartilage [16]. The EMA denies young patients treatment with advanced ACI products. Furthermore, the PIP inclusion criteria are inconsistent, demanding 16- to 17- [12], 14- to 17- [14], and 10- to 17-year-old patients [13].

Mumme et al. claim that remestemcel-L (Prochymal) data justify separate testing in “children”. Prochymal failed a phase III trial, but the primary outcome was significantly increased in paediatric graft-versus-host-disease. We still cannot define precisely how young and older cells differ. In contradistinction, a new breakthrough in acute lymphoblastic leukaemia (ALL) treatment was achieved by reprogramming T cells to destroy ALL cells [17]. Tisagenlecleucel is now approved for ALL patients <25 years old who relapse after chemotherapy. This age limit differentiates younger from older patients and appears to be reasonable. It is not a legal age limit. We agree that in younger patients’ the immune system is more flexible, but we re-

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spectfully disagree that Prochymal data support a general division of patients into adults and “children”.

The term “off-label” emerged in 1988 [18]. Regulatory approval prevents dangerous compounds from being sold as medicines. The on/off-label framework reflects a complex balance between drugs being developed and marketed commercially, the need to restrict drug promotion and physicians’ right and duty to prescribe for any indication [19]. Imposition of the on/off-label framework on administratively labelled “children” is a blur at the interface of physiology and law. For example, the field of paediatric oncology emerged “off-label” before this term even existed [2, 3, 5, 18, 20]. The EMA seriously claims off-label use of medications in “children” to be always dangerous [21]. Spherox is on-label from the 18th birthday on, off-label earlier, despite the fact that only the legal status changes overnight.

The discrepancy between a potential plethora of bioengineering and few EMA-approved products is rooted in a blur at the interface of law, science and drug approval. Instead of facilitating bioengineering, the EMA demands questionable and potentially harmful “paediatric” studies [2, 3, 5, 9, 20]. This is supported by apparently scientific justifications from learned societies [6], regulators [6, 22] and industry [23] without which the FDA/EMA could not continue their “paediatric” crusade. The European Society of Developmental Paediatric and Perinatal Pharmacology (ESDPPP) website praises these mandatory “paediatric” studies as a “paediatric imperative”; ESDPPP members are happy to help [24]. These studies ensure networking, publications and “paediatric” careers in academia, industry and FDA/EMA, while young patients do not benefit. They recruit worldwide, including in Switzerland [25].

Ethics committees should re-assess all “paediatric” studies, suspend questionable ones, and reject new ones if clinically and scientifically inappropriate.

**Disclosure statement**

No financial support and no other potential conflict of interest relevant to this article was reported.

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