"Comment on: A review of the experience with pediatric written requests issued for oncology drug products."
Young patients with malignancies need reasonable studies with therapeutic intention.

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To The Editor:

We read with interest "A review of the experience with pediatric written requests issued for oncology drug products".[1] The authors emphasize that children typically do not have the same cancer type as adults. But post-pubescent minors are physiologically more mature than neonates. We agree that developing promising new drugs in children is critical to

public health. Doubtlessy, the oncology written requests (WRs) reflected best intentions, but good intentions can result in poor outcomes.[2,3] Cobimetinib, dabrafenib, trametinib received WRs for melanoma. Their study data are listed as not yet completed.[1] No studies are www.clinicaltrials.gov-listed, and hopefully will never begin. Pediatric melanoma studies with ipilimumab and vemurafenib were terminated.[4,5] They offered monotherapy when combination therapy had become standard-of-care. As a result, recruitment waned.[6] Prepubertal malignant melanoma types exist. However, most minors with conventional malignant melanoma are adolescents and do not have "pediatric" melanoma.[6,7] The WR for docetaxel triggered an international "pediatric" nasopharyngeal carcinoma (NPC) study in patients ≤21-years-old.[8,9] NPC occurs also in minors, but is not a pediatric disease.[10,11] The WRs for single cytotoxics were issued although these were already successfully used in "cocktails".[12] These WR-triggered studies had no therapeutic intention, contrary to those performed by the pediatric oncology networks.[12] They aimed at "pediatric" labels.[13,14] The FDA justified such studies by emphasizing that study participation had become standard-of-care.[15] However, this is true only for reasonable studies.[13,14,16] The term "child" has two meanings. *Legally/administratively* it describes minors, who *bodily* mature from conception over birth until maturation with puberty.[14,17] Furthermore, puberty has accelerated.[18,19] The pediatric warnings that moved Shirkey to characterize children as "therapeutic orphans" had the *legal* purpose to protect manusfacturers against frivolous lawsuits in the litigious US.[13,14,20] Their kernel of truth were toxicities in premature newborns observed in the 1950s.[21] The "moral imperative" for "pediatric studies", expressed by the American Academy of Pediatrics,[21] is based more on morality than on science. It is semantically a blur at the interface of medicine and law and is maintained by conflicts of interest. "Pediatric" studies became a business opportunity for pediatric researchers, industry, commercial clinical research, and have advanced careers in regulatory authorities, research, and industry.[13,14,16] Not all cancers in minors are "pediatric". Pediatric oncology emerged when effective drugs already existed, took decades to reach today's successful results,[12] and worked "off-label" decades before this term emerged in 1988.[22] Today's innovative treatments engage the body's immune system. The youngest patient with acute lymphoblastic leukemia (ALL), the most frequent pediatric malignancy, was 6-years-old when successfully treated after relapsing after chemotherapy.[23-25] The FDA today recommends the inclusion of adolescents into adult cancer studies,[26] while the European Medicines Agency (EMA) expands "pediatric" demands into diseases that occasionally occur before the 18th birthday, e.g. hepatocellular carcinoma.[27] It is time to acknowledge that many regulatory "pediatric" studies are pointless and often harm, withholding effective treatment.[13,14,16] Institutional Review Boards/ ethics committees should reject questionable "pediatric" studies and suspend harmful ones. The FDA should re-consider questionable collaboration with the EMA in the "pediatric" cluster.[28,29] Long-term, pediatric legislation needs revision.[13,14,16]

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