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PEDIATRIC ONCOLOGY STUDIES TRIGGERED BY THE UNITED STATES (US) FOOD AND DRUG ADMINISTRATION (FDA) AND THE EUROPEAN UNION (EU) EUROPEAN MEDICINES AGENCY (EMA) AIM AT LABELS, NOT AT IMPROVED TREATMENT. SOME HARM YOUNG PATIENTS BY EXPOSING THEM TO SUBSTANDARD MONOTHERAPY INSTEAD OF COMBINATION TREATMENT

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Background Both FDA and EMA reward/demand pediatric oncology studies. Do they advance pediatric cancer care?

Methods We analysed publications of FDA representatives,^{1–3} FDA-triggered pediatric oncology studies in the literature and in www.clinicaltrials.gov,⁴ and FDA/EMA pediatric reports.^{5–6}

Results FDA authors express two key assumptions: (1) children, defined as < 17y, need separate proof of efficacy;^{1–3} (2) with the exception of chronic myelogenous leukemia, the biology of cancer in children is different from adult cancer.¹ FDA-triggered studies investigated single cytotoxic agents in heavily pretreated refractory/relapsed patients ≤ 21y.^{2–4} In these days, combination treatment with up to 13 cytotoxic agents was standard of care.⁷ Another round of treatment with a single chemotherapy agent did not increase survival, but rewarded companies with patent extension, researchers with publications, the FDA with labeled information. The EU expanded the definition of children to < 18y and demands ‘pediatric investigation plans’ (PIPs) also for rare diseases. One FDA-triggered package investigated ipilimumab in ‘pediatric’ melanoma; 13 EMA PIPs demand ‘pediatric’ studies in solid tumors including melanoma; two ‘pediatric’ monotherapy studies with ipilimumab and vemurafenib, respectively, were terminated in 2016, five others continue recruiting.^{3–4–8}

Discussion FDA/EMA-requested/demanded ‘paediatric’ oncology studies focus on labels in administratively defined ‘children’. FDA/EMA-used age limits are not physiological. FDA assumptions about different biology of ‘pediatric’ malignancies are incorrect.^{3–4–8–9} FDA/EMA reports list regulatory, not therapeutic achievements.^{5–6} Some EU researchers perform predominantly PIP-demanded oncology studies. In a cartel-like cooperation, the EMA demands such studies, threatening non-approval of life-saving drugs. Researchers and EMA representatives co-author lauding reports.¹⁰

Conclusion FDA representatives augmented the flawed ‘therapeutic orphans’ concept by additional wrong assumptions about ‘paediatric’ malignancies’ biology.^{1–4} The EMA further expanded the ‘Paediatric Imperative’. Also PIPs do not advance treatment. Ethics committees should be alerted to re-

analyze ongoing ‘pediatric’ studies, suspend questionable ones, and reject new ones. US+EU pediatric laws need revision.

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PREDICTION OF RALTEGRAVIR PLASMA CONCENTRATION IN HIV PAEDIATRIC PATIENTS USING PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL

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Background Raltegravir is a drug used to treat patients with HIV infection. Understanding the disposition kinetics including the ontogeny of the major metabolic enzyme (UGT1A1) is important in prediction of raltegravir pharmacokinetics in paediatric patients.

Methods Sim-Raltegravir compound file in Simcyp simulator version 18 was used to predict pharmacokinetics in paediatric subjects aged 4 weeks to 6 months, 0.5 to 2, 2 to 6 and 6 to 12 years. Details of trial design were matched as closely as possible with a clinical study.¹ Rate of absorption and variability in first order absorption model within Simcyp were set to the reported values. Predicted plasma concentration time profiles with 5th and 95th percentile were compared with observations.

Results The predicted vs. observed geometric mean area under plasma concentration-time profile of raltegravir was 18.4 vs. 22.3 µM.h in subjects 4 weeks to 6 months and 16.5 vs. 19.8 µM.h in those 0.5 to 2 years old. In 2 to 6 and 6 to 12 year olds around 80% and 85% of observed data were within 5th and 95th percentile of the predictions.

Conclusion The results show that the UGT1A1 ontogeny profile in the Simcyp version 18 adequately addressed age-related differences in pharmacokinetics of raltegravir.

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