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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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Disclosure(s) The author has worked for more than 20 years in research & development/medical affairs in pharmaceutical industry and is now an independent consultant, advising pharmaceutical companies and academic institutions in all aspects of pediatric drug development, organizing scientific conferences, publishing, & more. The author’s elder daughter is severely handicapped with a rare syndrome, which has biased him against empty governmental promises.

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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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P86 TREATMENT MODALITIES IN PERIPHERAL FACIAL NERVE PALSY IN CHILDREN AND ADOLESCENTS

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Background Bell's palsy is the most common type of peripheral facial palsy in pediatrics. Recent studies strongly support the combined therapy with corticosteroids (CS), antiviral drugs and vitamins B. Our study aims to assess the effectiveness of proposed therapeutic modalities, including the relation between the patients' recovery and their age, etiological factors and applied treatment.

Methods The retrospective analysis involved 88 patients (52 females/36 males), between 18 months and 18 years old; the average age was 11.7 years. Data was obtained from the documentation of patients hospitalized at the Clinic of Neurology and Psychiatry for Children and Youth in Belgrade, from 2000 to 2017. House Brackmann's scale was used for the assessment of disease course and outcome. Pearson's χ^2 test, Friedman's test and general linear model were applied for statistical data processing.

Results The majority of patients were treated with combined CS/vitamins (42.0%) and CS/antiviral/vitamins (17.0%), whereas CS only received 22.7% of patients, all with an appropriate physical treatment. The group of idiopathic paralysis makes 62.5%, while the incidence of symptomatic paralysis is 37.5%; however, the recovery rate between these groups has not been shown ($p=0.309$). Patients received CS therapy were divided into 4 groups: CS only, CS+antiviral, CS+vitamins B, and CS+antiviral+vitamins B. The statistically significant recovery was registered in each group ($p<0.001$); however, no difference was found between the groups in term of recovery rate ($p=0.865$). For the assessment of recovery period in relation to the age, the obtained p value was 0.054, a borderline level, suggesting a faster recovery of children at younger age.

Conclusion The acute one-sided mimic musculature weakness is mostly idiopathic. The effectiveness of the CS therapy was strongly supported, suggesting CS as a core treatment for the Bell's palsy. It has been shown the faster recovery of children at younger age.

Disclosure(s) Nothing to disclose

P87 THE SWISS ASSOCIATION OF PERINATAL PHARMACOLOGY, SAPP: GOALS

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Background The medicine of pregnant women practices to a targeted personalized approach, tailored to the specific characteristics and needs the implications of interdisciplinary work between healthcare stakeholders. *Perinatal pharmacology*

comprises the impact of substances (drugs, medications and others) in pregnant women, nursing mothers, the unborn child, the premature, the newborn baby and the breastfed baby. Most of the drugs are off-label used. In this field grand challenge for *Frontiers in Medicine* emphasizes the importance of translational medicine.

Aim The primary goal of SAPP has always been and remains the same: it is the link between medicine and pharmacy, between practice, clinic, research and health authorities, in order to increase the safety of medicines in the population of pregnant and breastfeeding women and their newborns.¹

Methods On December 6, 2007, an interdisciplinary team of 8 physicians and pharmacists founded the Swiss Association of Perinatal Pharmacology, SAPP. It collects and promotes new findings in the field of perinatal pharmacology.

Results Specialists from all areas of perinatal pharmacology work together in a scientific committee to develop and update evidence-based principles for work in everyday clinical practice (hospitals, doctor's surgeries, pharmacies). Today, around 200 members benefit from this, who can orient themselves in regular further training courses and basic documents (monographs of active substances, therapy recommendations based on original literature). The SAPP thus closes the gap resulting from the predominant off-label use and the resulting lack of information on drugs in this population.

Conclusion The primary objective of SAPP has been achieved - it provides guidance for the practitioners in the broad field of perinatal pharmacology and bridges the gap caused by the lack of drug approvals in this population. Long-term survival will be ensured by measures anchored in law.

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Disclosure(s) Nothing to disclose

P88 THE POTENTIAL IMPACT OF HEMATOCRIT CORRECTION ON EVALUATION OF TACROLIMUS TARGET EXPOSURE IN PEDIATRIC KIDNEY TRANSPLANT PATIENTS

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Background Tacrolimus is an important immunosuppressive agent with high intra- and interindividual pharmacokinetic variability and a narrow therapeutic index. As tacrolimus extensively accumulates in erythrocytes, hematocrit is a key factor in the interpretation of tacrolimus whole blood concentrations. However, as hematocrit values in pediatric kidney transplant patients are highly variable after kidney transplantation, translating whole blood concentration targets without taking hematocrit into consideration, is theoretically incorrect. The aim of this study is to evaluate the potential impact of hematocrit correction on tacrolimus target exposure in pediatric kidney transplant patients.

Methods Data were obtained from 36 pediatric kidney transplant patients. 255 tacrolimus whole blood samples were