Companies Need More Awareness Of EU Pediatric Investigation Plans (PIPs)

Pediatric legislation was introduced based on the American Academy of Pediatrics (AAP) concerns that children did not participate sufficiently in therapeutic progress. But child healthcare in our modern world has been continuously improving since world war II, and continues to improve. Of course, things can always improve further. But our concept of childhood is still based on the perception that children are under age, without sufficient consideration of how their organs mature during development. Children do not need the same clinical studies as adults, but studies that reflect our increasing understanding of their body and organs. Most EU pediatric investigation plans (PIPs) demand pediatric studies that are meaningless, unfeasible, both, or even worse. To give in to the EMA's demands not only puts children in danger, but also companies. EU PIPs have the potential of disastrous damage lawsuits. But this challenge also offers a strategic chance to re-calibrate drug development in the general public opinion.

When Shirkey characterised children as "therapeutic orphans", he referred to orphaning clauses, e.g. "not recommended for use in infants and young children", in the drug labels that emerged in the wake of new US pharmaceutical legislation of 1962. He noted that many physicians ignored them, warned that this might be difficult to defend in court, and demanded clinical pharmacology testing in minors.[25] Should physicians in these days have let little patients die because antibiotics were not licensed for use in children? While Shirkey was concerned for medical doctors in court and for the safety of small patients, the regulatory authorities (RAs) initially were not too concerned about pediatric off-label use. Also, physicians acted pragmatically within the new pharmaceutical legislative framework. Child healthcare has continuously improved. But we struggle with the conceptual framework.

In 1977, the AAP published first guidelines for the ethical conduct of drug studies in children,[1] followed by two revisions in 1995[2] and 2010.[3] The 1995 document explained that drug administration in "children" had occasionally led to toxic effects, including death. This statement was based on just two publications about drug in *premature newborns*.[2] Thus, the AAP "extrapolated" justified concerns for drug use in premature newborns into much less justified concerns for all pediatric age groups from newborns to adolescents. "Growth, differentiation, and maturation can alter the kinetics, end organ responses, and toxicities of drugs in the newborn, infant, child, or adolescent as compared to the adult"[2] was more a moralistic appeal than a data-based statement. The AAP's proclamation that "children have not shared in therapeutic advances to the same extent as adults"[2] was simply wrong, belied by the drop in children's death rates and the emergence of new specialities like neonatology or pediatric oncology. Maybe the AAP wanted children to benefit *more* from new drugs, but it didn't say so. Why?

Shirkey, drug manufacturers and the AAP used the contemporaneous *legal* term of children, but gave it a *medical* connotation. The AAP 1995 guidelines defined children as "persons who have not attained the legal age for independent consent to treatments or procedures involved in research, under the applicable law of the jurisdictions in which the research is conducted"[2] This was the contemporary understanding of the age of majority as opposed to childhood. Age of majority makes us responsible for most actions, including work, handling of property, marriage, crime, politics, sex, and warfare, as opposed to the age of minority, characterised by physical helplessness and dependency. [5, 27] In the 1960s, understanding dawned that children's bodies were different from adults, but details and consequences for drug dosing had to be worked out during the coming decades by pediatric clinical pharmacology (PCP), pediatrics, neonatology and pediatric oncology (PO). Shirkey on one side emphasised his concerns for *younger* children, but the term "therapeutic orphans" was used for children in general since it was coined in 1963.

Before world war II, there were few efficacious drugs apart from alcohol, opioids, and poisons. The thalidomide catastrophe of 1959–1962 revealed the potential horror of modern drugs' side-effects.[19] To balance efficacy and potential side-effects, RAs emerged as a new, powerful pillar in healthcare. Labels issued by RAs were not necessarily very specific. They became an obstacle that new compounds had to surmount to become broadly available.

There is broad agreement that modern labels are needed, but less about their use and limits in daily healthcare. A young general practitioner (GP) will use the label to dose anti-acne medication, while neonatologists' or oncologists' prescriptions are based on years of special training, with less regard of labels. RAs became a powerful pillar in healthcare, but didn't replace other channels of information handover. Medical doctors do not prescribe by studying labels, but from textbooks, supervised bedside training, conferences, consensus papers, sales representatives, and more. Most members of the different fractions in healthcare, including physicians, pharmacists, and regulators, are to some degree convinced that their respective role in healthcare is underestimated. The 1977 AAP statement noted that only 25% of currently available medicines were labelled for use in children.[1] It also emphasised that this didn't mean they were contraindicated or disapproved for use in infants and/or children, but also claimed it was unethical "to adhere to a system which forces physicians to use therapeutic agents in an uncontrolled experimental situation virtually every time they prescribe for children", and demanded drugs used in children be studied in children. The 1995 statement about kinetics, end organ responses, and toxicities of drugs in all age groups was repeated in 2010.[3]

In its 2001 report to congress, the FDA's wording oscillates between "more information about drug effects in children", "efforts to improve pediatric labeling information", and that most marketed drugs were not or insufficiently labelled for use in children,[8] referring to the AAP 1995.[2]

Children have to a considerable degree different diseases compared to adults. When Boklan complained in 2006 that research for children with cancer was less well funded than adult research,[6] the focus of her thinking was still how, somehow, adult research could be expanded into children. But a year later Boots showed that pediatric legislation enforces pediatric investigation in compounds that to a large degree target adult diseases.[7]

Little has changed, but we look back at ten lost years. Will the next ten years be lost again?

PCP has evolved on both ends of childhood. Very premature neonates survive. We know that most organs in absorption, distribution, metabolism and excretion (ADME) are mature already at the age of 2 years.[13] The AAP's "extrapolation" from preterm newborns to every minor was exaggerated, as is the claim that ADME is fundamentally different in all child age groups as compared to adults. Children are neither small adults nor another species. During adolescence, their body matures, and adult drug doses become adequate. The AAP lists on its website as pediatric age groups prenatal, baby (0–12 months), toddler (1–3 years), preschool (3–5 years), gradeschooler (5–11 years), teenager (12–18 years), and young adults (18–21 years).[11] ICH E 11 uses slightly different age groups.[12] The general claim that ADME in all age groups differs so fundamentally from adults that extra testing and clinical studies are required is not based on data, but on strong belief. If we go back to 1995, we see two roots: the contemporary *legal* definition of childhood suddenly used as a *medical* term, resulting in claims about ADME of the pediatric body from birth to adulthood that were not based on data. Secondly, an over-emphasis on clinical studies as opposed to common sense, clinical learning, and personal experience.[2] Within this logic, parachutes would be unsafe because they were never tested in randomised, double-blind, placebo-controlled trials.[26] There was never a catastrophe that enforced pediatric legislation, although employees of EU RAs try to conjure one when they speak of "lack of availability of appropriate medicines for children"[18] or "neglect of children in the development of effective and safe medicinal products".[15]

The consequences of equalising the legal border to adulthood with a medical border are even more visible in the EU pediatric legislation (EUPL). The majority of EU PIP-demanded pediatric studies reflect the belief that the entire population <18 needs the same studies as adults. Academia and the pharmaceutical industriy have so far not found an adequate answer to the threat this poses for children.[19] Industry and CROs are so far also failing to perceive the PIPs' danger for themselves. What will parents of a child with a rare[22–24] or a frequent disease[20] do when, after years, they realise that their child was harmed in a PIP-demanded study? They will sue without mercy, first the company that initiated the study, albeit coerced by the EMA, then institution review boards (IRBs)/ethics committees (ECs), hospitals, CROs, individual doctors and more. Two PIP-demanded harmful clinical studies in melanoma in adolescents had to be terminated in 2016, and this is just the tip of the iceberg.[19, 20, 22, 23]

You cannot fix a broken car by attending a yoga course. Confusion between *legal* and *physiological* definitions of childhood cannot be fixed by enforcing clinical studies in children, adolescents and young adults. The AAP should revise its definition of childhood away from the traditional legal understanding towards a physiology- and PCP-based understanding, differentiating between babies on one side and adolescents with an already adult body on the other

side. We need a re-calibration of the debate *which* studies minors need. The EU PIPs enforce studies copied from the adult clinical trials model on minors of all age groups. They are dangerous for children, companies and CROs. It will take a few years to get the first damage lawsuits through the courts, but they will come. Children do not need as many clinical studies as possible, but reasonable studies. Efficacy of drugs is, with few exceptions, if any, the same in adults, young adults and adolescents with an adult body. Where efficacy can be extrapolated from adults to school age children, this can be done by modelling & simulation, followed by small confirmatory pharmacokinetics/pharmacodynamics (PK/PD) clinical trials, and/or opportunistic studies performed when adult drugs are used therapeutically in minors.[10, 14, 16] Eventually, we will need a *legal* fixing of the confusion of the definition of childhood at the interface of law and medicine.

Modern labels were a first step in handling efficacious drugs for mankind's health. Both adults and children have so far profited, children probably even more so. We need next steps. Blind copying of adult regulatory requirements for diseases that are rare in children results in a multitude of unfeasible studies that abuse its participants as therapeutic hostages.[20] Instead, we need a different approach for rare pediatric diseases. "We" is the academic clinical community, industry, regulators, parents and patients. Pharmaceutical companies will need the help of IRBs/ECs to reject unfeasible and worse pediatric studies that the EMA is imposing on new drugs. Eventually, public pressure will help to convince the EU lawmakers to revise the legislation. More countries with drug development capacities are emerging. We need truly global approaches to let children benefit as much as possible from pharmaceutical progress.

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