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# Challenges and New Frontiers in the Paediatric Drug Discovery and Development

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## Abstract

Drug discovery and development advances in the last decades allowed to find a treatment for many preventable diseases. However, all too often, children are excluded from these progresses since most of the new medicines have been discovered and developed for the adult population. Even if paediatricians routinely give drugs to children 'off-label', researchers have demonstrated that children do not respond to medications in the same way as adults. Furthermore, certain specific disorders are unique to children or occur in children differently than in adults. Besides specifically testing medicines in children in proper clinical studies taking into due account the peculiarity of this population, there is a growing recognition of the need to develop paediatric medicines having in mind the specificities of this vulnerable population. In this chapter, we will provide an overview on the drug discovery and development path for children highlighting challenges and new frontiers of each phase from the discovery to the preclinical and clinical development as well as we will provide a slightest hint about paediatric biomarkers discovery, age-appropriate formulation, pregnancy, and perinatal pharmacology and *in silico* pharmacology. Finally, pricing and reimbursement policies for medicines and new and existing research initiatives in the field will be discussed.

**Keywords:** human development research, paediatric drug discovery, preclinical research, juvenile animal models, paediatric pharmacology, paediatric biomarkers, age-appropriate formulations, perinatal pharmacology, physiologically-based pharmacokinetic (PBPK)

## 1. Introduction

Even if paediatricians routinely give drugs to children 'off-label' (drug not specifically approved for use in children), it is known that children respond to drugs in a very different way than adults in terms of safety and efficacy [1]. Anatomical, physiological and developmental differences between children and adults and among children of different ages reflect in changes in absorption, distribution, metabolism and excretion (ADME). Moreover, less information is available in younger age groups and neonates. Furthermore, while certain specific disorders are unique to children, others could be more common in children than adults or infrequent in children compared to adults. Notwithstanding, children have been excluded from testing of new drugs for many years and for this reason have been defined as 'Therapeutic Orphans' by Shirkey in 1969 [2].

The lack of a regulatory framework that obliged to test medications in the paediatric population taking into account the specificities of children and the ethical concerns behind resulted in several examples of therapeutic tragedies in paediatric patients. A new liquid formulation of the antibiotic sulphanilamide was developed in 1938 to allow oral dosing for paediatric patients who could not swallow the tablet form. Unluckily, the solvent used to dissolve the active substance was a toxin that caused many adverse events with a 30% mortality rate [3]. And again, Thalidomide was marketed in Europe in the late 1950s for the treatment of nausea in pregnant women causing severe birth defects in thousands of children including severe shortening of the extremities, malformations of ears, heart, intestines and other structures, depending on the embryologic stage at the time of exposure [4].

These tragedies are just an example of the high risk to which children have been exposed for years and have led to the increasing awareness that new medications for children should be carefully studied before they could be approved, defining the proper requirements and ethical issues to guarantee efficacious and safer drugs for children. As a consequence, regulations have been adopted independently in the most developed countries, but in accordance with unified guidelines suggested by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), an organisation working on the harmonisation of pharmaceutical regulatory requirements within the European Union (EU), Japan and the United States (US) [5].

The European Paediatric Regulation was adopted in 2006 and entered into force in 2007 [6] imposing to pharmaceutical companies developing drugs of potential interest for children to prepare a paediatric investigational plan (PIP) to obtain a marketing authorisation for an indication in adults, unless they were granted a product-specific waiver by the Paediatric Committee of the European Medicines Agency (EMA), for example if the indication does not occur in children [7]. The paediatric regulation has defined rules concerning the development of medicinal products for paediatric use and introduced rewards and incentives for the development of paediatric drugs (i.e. the paediatric-use marketing authorization—PUMA) [5].

In the US, two main acts have complemented each other ruling the evaluation of drugs in infants and children and increasing the paediatric clinical studies and drug labelling for children: the PREA of 2003 [8] and the BPCA of 2002 [9], both amended in the FDAAA of 2007 [10]. A different approach has been taken in Japan, more focused on premiums granted to pharmaceutical companies as rewards for developing paediatric medicines without a regulatory framework specifically addressing paediatric clinical research. As an effect of these premiums, the price of those drugs is not reduced as normally occurred every 2 years in the Japanese system [11].

## **2. Paediatric diseases**

A major challenge in studying paediatric diseases is the relatively low incidence rate or uniqueness of some disorders in children. Paediatric diseases may resemble those in adults, but considerable differences may also exist with regards to aetiology, progression, comorbidities and prognosis [12].

Several cancer types are genetically different in children compared to adults as demonstrated by a comprehensive analysis of genetic alterations in a pan-cancer cohort including 961 tumours from children, adolescents, and young adults, and comprising 24 distinct molecular types of cancer [13]. Epilepsy in children is associated with a wide range of congenital or hereditary diseases, while in adults, it is associated mainly with strokes and brain tumours [14]. The onset of systemic lupus erythematosus (SLE) during childhood is associated with different clinical

manifestations and two to three times higher mortality compared to adult-onset SLE [15]. Moreover, frequent comorbidities are specific of premature neonates including persistent ductus arteriosus, sepsis, intra-ventricular haemorrhage and necrotising enterocolitis, and mortality is the highest in premature neonates born <28 weeks' gestation [16, 17].

The above studies provide just some examples of how children and adults can be differently affected by similar diseases underlining the importance to address the drug discovery and development process starting from the specificities of the paediatric population.

## **2.1 Changes occurring during development and age groups**

Obviously, childhood is the period of life when the physiological and physical changes are the most important and the fastest. Physiological systems and functions are immature in neonates at birth with the degree of immaturity depending on gestational age. These systems develop progressively and changes can be observed, for example, in gastrointestinal motility and function, body composition and size, activities of transporters and metabolism enzymes, and renal function. The process is dynamic and nonlinear with progressive rapid growth and maturation in the first weeks/months of life, and slower thereafter. These developmental changes affect drug disposition, as discussed later, with differences among neonates, children, adolescents and adults [18, 19].

Therefore, defining the paediatric population is a very complex issue since it represents an extremely heterogeneous population. To address the peculiarity of each age group and to provide guidance for regulatory and clinical matters, the international regulation on paediatric clinical trials [20] has described four subsets: pre-term and term neonates (0–27 days), infants (1–23 months), children (2–11 years) and adolescents (12–18 years). In addition, the recently revised EMA guideline 'Ethical considerations for clinical trials on medicinal products conducted with minors' issued on September 2017 has further sub-divided the age group 2–18 years into pre-schoolers (2–5 years), schoolers (6–9 years) and adolescents (10–18 years) [5, 21]. It has to be underlined that this definition, although useful to unify the system of rules and law in this field, does not always reflect the maturity of the child, which is something that is generally recognised as crucial aspect to be taken into account during the conduct of paediatric clinical trials [5].

## **2.2 Rare diseases**

When it comes to talking about paediatric diseases, we cannot exclude the rare disease field since many rare diseases are diagnosed during childhood. Rare diseases include a very heterogeneous group of disorders, affecting any body system. A disease is defined rare if it affects fewer than 1 in 2000 people in Europe and fewer than 200,000 people in the United State. A high percentage of rare diseases (about 80%) affect children, and in 50% of cases, all rare diseases are characterised by a childhood-onset with a significant impact on the well-being of the patients and families [22–24].

Although rare diseases have by definition a low prevalence, with some having a single identified case worldwide, collectively they affect about 6–8% of the human population with a number of diseases recognised as rare comprised between 6000 and 8000 diseases [25].

Despite the high impact they have on the worldwide population, few treatments are available on the market. Drug development for rare diseases poses unique scientific and ethical challenges, most of which in common with the obstacles described

in this chapter for the paediatric population. Since they affect a small population, heterogeneous and widely dispersed, it is more difficult to enrol enough patients in clinical studies and pharmaceutical company shows a scarce interest in this field for the low return they may have.

Moreover, considering the high incidence and prevalence during the childhood, the ethical issue is predominant in this field. And additional challenges may result from the frequently progressive, life-limiting or life-threatening nature of these diseases.

As described below, new approaches in all the phases of the drug development process may offer valuable solutions to overcome these difficulties in the rare diseases as well as paediatric diseases field.

### 3. Tailored drugs for children

Drug discovery and development path represents the long process starting with the identification of new target molecules (discovery phase), going through studies on microorganisms and animals (preclinical development) and finally testing the new medicines in the target population (clinical development) to bring them to the market (authorization and commercialization). Considering the differences between children and adults above mentioned, a new drug to be used in children should be specifically tested in children themselves in controlled clinical studies. At the same extent, medicines for children should be developed having in mind the specificities of this vulnerable population starting from the very initial phase of discovery.

#### 3.1 Drug discovery

In order to make available better medicines for children, it is mandatory to start thinking differently from the beginnings of the long process of drug development and stop the habit to translate results from adult to children. Even if we cannot deny the potentialities and advantages of using existing drugs in alternative ways or populations, as the case of repurposed drugs or the use of extrapolation in paediatric drug development, these approaches should be considered complementary to a drug discovery tailored to children and not the only way to go.

Drug discovery for children should be focused on specific targets for paediatric indications and should not be influenced by the existing knowledge for adults. Appropriate preclinical animal and cellular models should be used, and new emergent technologies should be implemented.

The main challenges in the research of novel medications for children come from a range of unique characteristics of this population. As highlighted before, several paediatric diseases are unique of childhood or differ in children compared to adult. Therefore, it is of major importance to increase our understanding of the disease mechanism in children and of the human development mechanism relevant for paediatric diseases and use this knowledge to favour a proper drug target selection and validation. For this aim, the availability of adequate disease models, both at *in vitro* and *in vivo* experimentation level, is a critical factor.

The existing human cell lines are frequently derived from adult sources, making them inappropriate as *in vitro* model of paediatric diseases. Indeed, several studies have highlighted the differences existing between adult and foetal/neonatal cells. Differences in platelet transcriptome [26] and proteome [27] have been described between platelets derived from healthy adults and full-term neonates. Variations between neonatal and adult fibroblasts and keratinocytes have been described as probably associated with improved wound healing during the early neonatal period [28].

Xu et al. provided an overview on the *in vitro* models used to study paediatric brain tumours underlined that in the initial drug screening for new therapies, it is critical to use cell lines more closely related to the tumour and organism being studied. The authors listed 60 paediatric brain tumour cell lines reported in the literature, of which only a small number can be obtained from central repositories such as ATCC [29] or Children's Oncology Group (COG) [30], thus rendering more difficult for the research community to have access to the most adequate cell lines [31].

Considering these findings, novel preclinical models should be evaluated as platform for drug discovery for paediatric diseases, such as induced pluripotent stem cells (iPSCs) or innovative techniques including organoids and organs-on-a-chip. Disease-specific iPSCs represent a promising platform to understand pathological progression in patient-derived cells presenting many advantages: iPSCs are an unlimited source of patient-specific cells for drug testing and for the development of personalised medicine [32]. Advances in human pluripotent stem cell (hPSC) or tissue-resident adult stem cell (AdSC) research have led to the possibility to mimic any tissue in the human body through three-dimensional (3D) model including organoids and organs-on-a-chip that can be used as *in vitro* screening models [33]. However, to confirm the adherence of these *in vitro* models with their normal counterparts *in vivo*, we need a much deeper understanding of the physiology of human development than what is currently available.

In addition, as regarding the animal models, the number of comprehensive studies describing the normal development of different physiological systems and processes in laboratory animals from molecular to system levels is very limited, and such studies usually do not exist in animal models of paediatric diseases. Thus, questions of comparability of developmental stages across species continue to create debate. The need to use juvenile animal models will be better discussed in the following section.

In addition to the need of developing cellular and animal models more suitable to study paediatric diseases and the instruments to work with immature animals, all the new emergent technologies should be timely applied to the paediatric drug discovery in order to speed up the pharmacological research, including pluripotent stem cell, 3D cell cultures, target validation, patient-derived cell assays, microfluidics, high-throughput cell image analysis, non-invasive drug delivery systems and devices to measure drug safety or efficacy non-invasively.

### 3.2 Preclinical development

Commonly, only a small number of compounds identified in the initial discovery phase will pass through to more rigorous preclinical development. Pre-clinical studies—*in vitro*, *in vivo*, and *ex vivo*—are essential steps in the drug development path to provide detailed information about the pharmacokinetic (PK) and pharmacodynamics (PD) properties of the selected molecules. The main goal of this phase is to improve the understanding of the drug properties *in vivo*, evaluating their efficacy, biodistribution, toxicity involving multiple experts, and competences from pharmacologists, drug metabolism specialists, chemists, toxicologists and formulation experts.

Drug dosing and response may differ markedly between adults and children for many reasons: anatomical and physiological differences between paediatric and adult population [34, 35], different diseases or presentation of diseases [36], differences in PK and/or PD profiles [37], different 'host' responses [38] different adverse drug reactions [39] and drug formulation.

There are many examples of drugs with a diverse PK profile in children compared to adults as a consequence of a different absorption, distribution, metabolism

and excretion (ADME) [40]. The rate and extent of the bioavailability of a drug may vary as a consequence of the developmental changes that occur in absorptive surfaces, especially the gastrointestinal tract. Dissimilarities have also been reported in drug metabolism, transporters expression, biliary function and renal clearance, resulting in differences in drug disposition and elimination [41].

Similarly to PK profile, PD profile is also affected by human development and drug targets may vary under developmental control: their level of expression, affinity or activity may diverge according to the patient's age, resulting in variable drug responses depending on patients' age group. This is particularly important in younger infants, more vulnerable to drug toxicity and related adverse events by modifying drug therapeutic windows [42].

Another aspect to be taken into due account is represented by the effect of the ontogeny and genetic variation interactions on drug response, known as pharmacogenetics [43]. Several pharmacogenetics studies have indeed demonstrated the differences in response to drugs between children and adults [44].

To take into consideration these aspects, age-appropriated technologies and models in paediatric drug development should be applied: appropriate cellular models, juvenile animal model, administration of sub-pharmacologic doses (micro-dosing) to evaluate PK in a first-in-paediatric study, modelling and simulations and pharmacogenetics biomarkers.

Juvenile animal models should be used to take into due account the specificities of the paediatric population as described above and to fill the gap between developmental and mature toxicity. Indeed, the same drugs can have a different safety profile in children compared to adults due to many aspects such as body weight, developmental differences in growth and function of target organs, immune system maturation and different expression of receptors system. For example, adult models of epilepsy cannot be simply applied to the study of paediatric epilepsy and key differences exist in human and rodent brain maturation process [45].

Extrapolation of data from adults or studies using adult animals is not always adequate to predict these differences in safety profile for paediatric age groups. For this aim, 'Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications' has been adopted in January 2008 by the EMA. The guidelines recommend the 'use of juvenile animal models when a drug safety cannot be appropriately defined in the intended paediatric age group on the basis of human data or previous animal studies' and provide recommendation on the 'timing and utility of juvenile animal studies in relation to phases of drug development process'. In particular, the document points out that studies in juvenile animals should be performed on a case-by-case basis rather than using standardised study protocols and describes the key aspects to take into consideration in the study's design: age of the animal and duration of the studies, route of administration, selection of species, PK and toxicokinetics, dose selection, endpoint [46]. Juvenile studies are especially recommended when it has been demonstrated that a medicine causes toxicity in adult at the target organ level and/or to tissues that undergo significant post-natal development (CNS, immune, or reproductive systems). As also underlined by Anderson et al., it is important to conduct the preclinical experiments in the most appropriate species at the most relevant age on the basis of comparability of the specific organ system development in question [47]. And many issues have to be considered in juvenile toxicology studies: difficulties in the dose administration due to the small size of the animals, in blood and tissue sample collection, and in distinguishing direct versus latent effects [48].

Therefore, proper animal models should be developed. As an example, Lohi et al. described the zebrafish as a model for paediatric diseases, with particular

emphasis on haematopoietic and infectious diseases [49]. In this direction, several zebrafish models for the study of leukaemia have been developed [50–52].

Preclinical data obtained from juvenile studies, extrapolated assuming a correlation between developmental growth in animals and children, can be linked to different information from a variety of data sources using the modelling and simulation (M&S) approach.

M&S is a multidisciplinary science, which integrates knowledge about diseases, drug characteristics, *in vitro*, *in vivo*, and *ex vivo* data, patient populations and clinical trial parameters in order to optimise study design and drug labelling [53]. Modelling and simulation tools have long been used in drug development to allow a quantitative assessment of age- or growth-related differences in drug effects and consequently the potential implications for different paediatric age groups [54]. On this basis, software has been created to link *in vitro* data to *in vivo* ADME and pharmacokinetic/pharmacodynamic (PK/PD) outcomes in order to predict the potential clinical complexities prior to human studies [55].

The use of a model-based approach in the paediatric context provides several advantages allowing the integration of prior *in vitro* data and physiologically based pharmacokinetic (PBPK) models with pharmacodynamics (PD) models (PBPK-PD models) and the optimization of experimental protocols. Finally, this approach improves the accuracy and efficiency of data extrapolation and allows the reduction in the number of animals per experiment that sometimes may also be replaced by *in silico* experiments.

### 3.3 Clinical development

Finally, efficacy and safety of the new medicine should be tested in appropriate clinical trials. When it comes to the clinical development of a drug, several issues related to the peculiarity of the paediatric population have to be faced. Conducting a paediatric clinical trial raises several scientific and operational challenges.

First of all, the low prevalence of many paediatric diseases leads to a limited number of children affected by each condition. In addition, the ethical issues are also to be considered to obtain clinical benefits for children assuring the best possible protection for these vulnerable subjects. Moreover, considering the heterogeneous nature of the paediatric population, the population subsets to be included in a study should be chosen with great attention in order to be sure to consider the most likely target population for the medicine being tested.

Another issue to be considered in the design of a paediatric clinical trial is the lack of tools and/or methods for quantitative and qualitative assessment tailored for the paediatric population and its sub-groups (study endpoints, questionnaires and scales for the measurement of psychophysical parameters and tools for the assessment of adverse reactions).

The difficulties described above, in testing appropriate drugs in children, have brought to an increased use of off-label drugs with high risks for adverse safety events and efficacy failures and to a general knowledge gap in paediatric research [1].

The US and EU Regulatory agencies foster the drug clinical development through regulations and incentives and the increasing number of paediatric trials and specific label changes and dosing recommendations.

Ground-breaking methodologies such as innovative trial design, application of modelling and simulation and other tools supporting paediatric trials (such as specific outcomes measures, biomarkers, statistical methods, etc.) can help researchers to overcome obstacles faced in planning, initiating and conducting a clinical trial involving children.

For example, to reduce the number of samples required for a study, sparse and scavenged sampling approach can be used. Sparse sampling uses a lower number of samples per patient compared with traditional PK sampling methods. Scavenged sampling consists in the use of residual blood/plasma samples remaining after the laboratory tests obtained in the course of medical care. These approaches reduce the risk for the child and eliminate the need for vascular punctures specifically for the study and, as a consequence, increase the rate of parental consent and the availability of several samples per infant [56].

Statistical methods, such as the Bayesian design, allow the extrapolation of results out of fewer children than in the conventional, fixed-number design, also considering evidences in adults [5].

Modelling and simulation approaches allow to successfully predict the optimal dosing regimens from the preclinical to the clinical phase [57].

More innovative trial design methods are being developed to overcome the limits related to small samples and to the acceptability of the trial. These alternative approaches, limiting the amount of experimentation in children, represent a promising way of ultimately improving paediatric care [58].

### **3.4 Paediatric biomarkers**

A biomarker can be defined as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention’ [59].

Biomarkers can be influential in every phase of drug development, from drug discovery and preclinical development, through each phase of clinical trials and into post-marketing studies. Evaluation and application of biomarkers can be useful to refine a drug dose or dose interval, or to select the appropriate population during early-phase clinical development of a product [60].

Despite this, the discovery of paediatric biomarkers has been limited and to cover the resultant gap, extrapolation, in children, of biomarkers identified and employed successfully in adults has become a common practice. However, human development impacts almost all factors and systems from organ function to drug disposition including the commonly utilised biomarkers that are influenced by changes occurring from birth onwards [61]. Therefore, adult biomarkers are not always appropriate to a paediatric setting.

A major challenge in the paediatric biomarkers discovery path is the sample availability due to the low prevalence of many paediatric diseases. Moreover, compared to adults, the paediatric populations is more heterogeneous making more difficult to obtain samples for biomarker discovery and validation, with the patients often distributed among several centres. Consequently, multicentre collaborations are often necessary in order to access sufficiently large study populations of affected children to generate big enough datasets to adequately power research studies [62].

Additional obstacles in children are represented by the difficulty to obtain appropriate age-matching control samples in order to minimise the influence that age-related changes may have on biomarker discovery and validation. Research on healthy children is generally restricted to minimal risk procedures, so although biological samples like saliva and urine can be relatively easy to obtain, blood samples are difficult to obtain in healthy children, particularly in neonates [61].

Moreover, several ethical considerations have to be taken into due account to enrol children in a biomarkers study: an effective and simplified consent process, long-term retention of samples for future research, the impact of ancillary genetic information on family members and predisposition to adult-onset disease [61].

Current advances in molecular techniques and the speed up of the ‘-omics’ technologies (i.e. genomics, transcriptomics, metabolomics and proteomics) have provided new tools facilitating the discovery of new biomarkers. The promise of omics technologies is considered huge, but translation of these technologies into clinical setting has been quite slow especially in the paediatric field.

### **3.5 Age-appropriate formulation**

The effect of age on PK profile, as discussed above, leads to different dosing requirements for different age groups. The proper dose administered may vary nearly 100-fold during childhood as a consequence of the body size and weight increase from birth to adulthood [63]. Premature neonates admitted to the hospital can weigh as little as 500 g. Moreover, since the maturation process in children is not linear, not always a linear relationship exists between a medication dose and body size and/or weight.

The need to have safe and suitable drugs for children has led to the awareness that drug formulations tailored to children in all the target age groups is essential. Formulation acceptability differs across age groups as children gradually develop their cognitive and motor skills, and improve their ability to swallow medications. And taste of a drug may be critical to ensure acceptable adherence to paediatric oral formulations.

The ideal formulation for children should have flexible dosage increments and minimal excipients, be palatable if given oral, easy and safe to administer, and be stable with regard to light, humidity and heat.

Continuous effort in formulation science by academic and paediatric researchers and commitment of policy makers and regulators should promote the preparation of pharmaceutical formulations for paediatric use, focusing on age tailored forms, excipient-related toxicity and safety risks in order to improve acceptability and facilitate medication adherence in children.

### **3.6 Pregnancy and perinatal pharmacology**

Up to 80% of women receive at least one medication, over-the-counter (OTC) or prescribed, during pregnancy in Europe [64]. The most common drugs used during pregnancy are anti-infectives and respiratory drugs [65]. It is recognised that medications assumption during pregnancy can represent a risk for the foetus, and therefore, medication use is approached with caution by pregnant women and their health care providers [66]. Nevertheless, the majority of current therapeutics used were never being studied in pregnancy for many reasons. Traditionally, pregnancy usually represents an exclusion criterion for phase I testing studies and women of childbearing age are usually excluded from clinical trials. Moreover, pharmaceutical companies manifest a low interest in the pregnant population since this population has more medico-legal risks and ethical concerns and represents a small percentage of the patient population that these companies target [66].

Due to the lack of studies involving pregnant women, safety drugs profile is usually obtained from either post-marketing surveillance or late-stage retrospective studies and efficacy and dosing data can be extrapolated from studies conducted in men or non-pregnant women [66].

To foster the availability of more effective and safer obstetrical drugs, a better understanding of the changes that occur in the mother, placenta and foetus is essential and strategies to monitor the therapeutic progress have to be improved [65].

The placenta represents a maternal-foetal interface between the mother and baby’s blood and controls exchanges of nutrients, oxygen, wastes and drug transport. The process regulating molecular transfer across the placental barrier is poorly understood leading to a lack of precious information for the drug development process.

Most studies on human placental biology have been conducted on tissue obtained after term delivery, or earlier, often from pathological pregnancies at various stages of disease, or from *ex vivo* model system. Less information can be obtained about the earlier phases of gestation and the normal development and functions of human placenta [67]. Behind these difficulties in obtaining the tissue, the studies on placenta require high level of expertise. To overcome these limitations, some initiatives have been undertaken. A 3D *in vitro* model of human placenta has been developed by a research group at the University of Vienna. The 3D model shows self-organisation, self-renewal and constant growth capacity and can be also pharmacologically and genetically manipulated allowing to study the physiological and pathophysiological processes of human placenta [68]. Another attempt to develop a model of human placenta has been carried out by the Huh Lab at the University of Pennsylvania, which developed the first placenta-on-a-chip to study drug delivery to the placenta and preterm birth. It consists of a small block of silicone that contains two overlapping layers of microchannels that are lined with trophoblast cells isolated from the outer surface of the placental barrier and separated by a porous membrane [69]. These advancements will allow a better understanding of the transport processes through the placenta and a better designing of new obstetrician drug.

### 3.7 *In silico* pharmacology

In the last decades, advances in computer technology has led to an increase in the use of informatics and bioinformatics in biomedical research, moving into an *in silico* era. The introduction of the *in silico* methods in the drug discovery and development has provided the opportunity to simulate every stage of the process, from preclinical to clinical, allowing to combine various heterogeneous types of data into computer-based pharmacological model.

As an example, *in silico* methods have been applied successfully in 2003 to drug screening when two different research groups found an identical molecule as inhibitor for the TGFb-1 receptor kinase: one using conventional 'wet-lab' assays and the other using an *in silico* approach [70]. In parallel, computational methods for drug development began to emerge, in order to model the interactions between drugs and biological systems [70].

This approach has been translated in paediatrics as a promising method to support the design of *in vivo* studies in the early phase of drug development. Johnson et al. predict with reasonable accuracy the *in vivo* drug clearance of 11 drugs that are commonly used in neonates, infants and children using *in silico* prediction methods and in particular the Simcyp<sup>®</sup> software [71]. Using a similar *in silico* approach, a physiologically-based pharmacokinetic model (PBPK) was developed in PK-Sim v4.2<sup>®</sup> to predict lorazepam PK in children as a function of age [72].

The introduction of PBPK modelling software in the field of paediatric drug development presents many advantages considering the peculiarities of this population. Notwithstanding these approaches could not replace totally the need for clinical trials, but they could reduce the amount of clinical trials required in children providing a primary exploratory investigation of drug PK, first-time dosing in children and study design [71, 72].

## 4. Pricing and reimbursement policies

The issues linked to the pricing and reimbursement of drugs administered to paediatric population are strictly linked to the mechanisms of drug marketing. Multiple factors are involved, and alteration of the regulatory environment can

rapidly change the drug development pathway chosen by pharmaceutical companies. At the moment, most of the drugs used for children have a marketing authorization for adults and are used 'off-label'. No incentives are present for a company to perform further studies in a paediatric population if the drug is used and reimbursed all the same.

The introduction of regulatory requirements for clinical studies in paediatric populations [6, 8, 9] has altered this paradigm for the newest drugs but has not changed the situation for the already used ones.

A basic principle for price calculation is the pay for quality-adjusted life years. Theoretically, this approach should increase the value of a new paediatric drug, but if the same drug is also used for an adult population, the payer would limit the price as a larger population is involved. In fact, due to the age stratification of the paediatric population, many paediatric pathologies might be considered as a rare disease. In fact, due to the facilitation linked to the development of a drug for a rare disease, an emerging approach from commercial entities is to develop drugs for the smaller paediatric population and to ask for an extension of the marketing licence to the adult group only when the licence is going to expire in a reverse approach to maximising the revenues for each new drug.

As this is applicable to all small populations, the regulatory agencies are already eliminating the rare diseases from the groups receiving extra benefit during the marketing authorization process, further complicating the issue.

Overall, due to the personalised medicine approach stratification, there is a strong need to increase the public funding during the early stages of drug development in order to not only reduce and control the cost of new drug but also encourage the development of new class of drugs based on the increased knowledge of the human normal and pathological development.

## **5. New and existing research initiatives in the field**

The advancement of innovative technologies in the paediatric pharmacology and preclinical phase of drug development will contribute to speed up both the development of new medicines for children and the paediatric clinical research. The awareness about the limited application of the innovative technologies in the paediatric drug development process and the scarce availability of safer and efficacious drugs for children has led, over the last years, to the onset of initiatives and collaborative efforts in this field.

At European level, we can cite EnprEMA [73], a network of research networks, investigators and centres with recognised expertise in performing paediatric clinical studies, which have greatly contributed to increase availability of medicines authorised for use in the paediatric population, according to what foreseen in the Paediatric Regulation. The TEDDY Network of Excellence (*European Network of Excellence for Paediatric Clinical Research*) [74], funded within the Sixth Framework Programme of the European Commission as *Task-force in Europe for Drug Development for the Young* and recognised as category 1 network member of Enpr-EMA, aims to favour adequate health policies and a social awareness on the importance of the paediatric medicines across Europe. TEDDY network goal is to support the paediatric clinical pharmacology and reduce the current fragmentation in the development of medicine in children. In line with this goal, TEDDY set up the European Paediatric Medicines Database as a pan-European source of information that includes data on paediatric medicines authorised by EMA collected by several sources (national authorities, regulatory bodies and pharmaceutical companies). Among other initiatives, we can mention the Conect4Children (C4C) IMI2

(Innovative Medicines Initiative 2) project [75] and the PedCRIN project [76]. C4C is a European project aimed to implement an infrastructure of clinical sites organised as a pan-European network to test medicines through well-organised, monitored and evaluated profit and non-profit paediatric clinical trials. PedCRIN project is intended to develop tools and actions for paediatric and neonatal trials in order to better address the real needs and gaps of the paediatric research community.

Behind the initiatives mentioned above, other actions have been taken to foster the early drug discovery and preclinical development phases. In this field, we can mention the European Paediatric Translational Research Infrastructures (EPTRI) project [77], aimed to design a research infrastructure (RI) completely dedicated to paediatrics to be included in the landscape of the ESFRI RIs. EPTRI aims to be complementary and fully integrated in the context of the existing RIs providing services, competences, expertise in the paediatric drug discovery and development. EPTRI will provide support to the paediatric research community through its thematic platform: Human Development and Paediatric Medicines Discovery, Paediatric Biomarkers and Biosamples, Paediatric Pharmacology, and Paediatric Medicines Formulations and Medical Devices. Through them, EPTRI will promote a translational approach from the bedside to the bench side, to make available more efficacious and safer drugs for children. In the formulation field, it has to be mentioned that the European Paediatric Formulation Initiative (EuPFI) [78] is a consortium working in a pre-competitive way on paediatric drug formulations and aimed to speed up the development of better and safer medicines for children by identifying issues and challenges in paediatric formulation development. EuPFI has set up the database Safety and Toxicity of Excipients for Paediatrics (STEP) that provides updated information on excipients safety and toxicity in children.

To address specifically the rare diseases, the European Joint Programme Rare Disease (EJP RD) [79], recently founded by the European Commission, brings over 130 institutions from 35 countries to create virtuous circle among research, care and medical innovation in the rare disease landscape. In particular, the project will improve the integration, the efficacy, the development and the social impact of research on rare disease and will implement an efficient model of financial support for all types of research on RD (fundamental, clinical, epidemiological, social, economic and health service), providing support to accelerate the exploitation of research results for the benefit of patients. To more specifically focus on the drug development in rare diseases, a task force has been created within International Rare Diseases Research Consortium (IRDiRC) [80], the Orphan Drug Development Guidebook Taskforce, aimed at providing support to academic and industrial drug developers and describing the available tools and initiatives specific for rare disease drug development [81].

As described, many initiatives exist as a result of the growing understanding that children cannot be considered as small adults, but need to be addressed specifically in the drug development path. But more efforts and the involvement of the national and international policy bodies are still needed to make the development of medicines for children a priority.

## **6. Conclusion**

Children represent particular vulnerable subjects and therefore should be protected and preserved by the risks that a clinical research can entail. However, at the same time, higher risks in term of major toxicity and/or reduced efficacy can result by the administration of drugs not properly tested and developed for them. Despite this, the off-label drug administration is still common in the paediatric population and children have been considered for year as the therapeutic orphans due to the

recognised lack of medicines specifically targeted for them. Moreover, the enormous progresses and advancements reached in the pharmaceutical field have not been applied to the paediatric population at the same extent of the adults.

The gap in the availability of proper medicines for children can be traced back to ethical, practical and economic reasons. As discussed in the chapter, the main practical reasons can be associated with the differences existing in the diseases affecting children compared to adults, as well as in the different physiology itself of the children compared to adults, the low number of patients affected, the need to take into account different age groups and the need to make available appropriate formulations. Moreover, the ethical concerns make more difficult to obtain the parents' consent. In addition, the pharmaceutical companies are not interested in this niche market, since they cannot foresee an adequate economic return. Furthermore, more challenges have to be faced when considering paediatric rare diseases. Complex aetiology, small affected population and subsequently small market size, high cost, and possibly low return on investment led to a large gap between basic research and patient unmet needs for rare disease drug discovery.

Many initiatives have been taken over the years, also at institutional levels, to promote a 'good research' in the paediatric field, in order to involve children and at the same time preserve them by unnecessary risks. Only increasing our understanding about human development processes and about how these processes impact on the onset and progression of diseases will allow us to develop specific medicines targeted for children. The knowledge of these processes will allow us to transfer in the paediatrics all the advancements and innovative technologies nowadays available in the adults' pharmacological research. Thus, more efforts are needed in terms of capitals, human resources, and technological expertise to speed up both the preclinical and clinical drug development in children and make available to children new medicines and appropriate treatments.

## Conflict of interest

The authors declare that they have no conflict of interest.

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