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GIENS WORKSHOPS 2022 / *Organisational and regulatory aspects*

Paediatric drug development and evaluation: Existing challenges and recommendations☆

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Summary Despite various international regulatory initiatives over the last 20 years, many challenges remain in the field of paediatric drug development and evaluation. Indeed, drug research and development is still focused essentially on adult indications, thereby excluding many paediatric patients, limiting the feasibility of trials and favouring competing developments. Off-label prescribing persists and the development of age-appropriate dosage forms for children remains limited. Against this background, the members of this panel (TR) recommend the launch of multi-partner exchange forums on specific topics in order to focus new drug research and development on the real, unmet medical needs of children and adolescents, and in keeping with the underlying mechanisms of action. Scientific information sharing and cooperation between stakeholders are also essential for defining reference evaluation methods in each medical field. These forums can be organised through existing paediatric facilities and research networks at the French and European level. The latter are specifically dedicated to paediatric research and can facilitate clinical trial implementation and patient enrolment. Moreover, specific grants and public/private partnerships are still needed to support studies on the repositioning of drugs in paediatric indications, and pharmacokinetic studies aimed at defining appropriate dosages. The development of new pharmaceutical forms, better suited for paediatric use, and the promotion of resulting innovations will stimulate future investments. Initiatives to gather observational safety and efficacy data following off-label and/or derogatory early access should also be encouraged to compensate for the lack of information available in these situations. Finally, the creation of Ethics Committees (EC) with a specific ''mother-child'' advisory expertise should be promoted to ensure that the current regulation (Jardé law in France) is implemented whilst also taking into account the paediatric specificities in medical trials.

Abbreviations

ASMR	actual medical benefit (*amélioration du service médical rendu*)
CIC	Clinical Investigation Centers
CRCs	Clinical Research Centers
CROs	Contract Research Organisations
CUA	compassionate use authorisations

EC	ethics committees
EEA	early access authorisations
EMA	European Medicines Agency
HTA	health technology assessment
MA	marketing authorization
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PUMA	paediatric use marketing authorisation
RT	round table
RWA	real world evidence
SmPC	summary of product characteristic
SPC	supplementary protection certificate

Introduction

The development of medicinal products for children and adolescents under 17 years of age is currently regulated by the EU Paediatric Regulation (EC) No 1901/2006 on medicinal products for paediatric use that came into force in 2007 [1,2]. This Regulation aims to improve the quality and ethical framework of research in children, to increase the number of drugs authorised for paediatric use and, failing that, to improve the data on drug efficacy and safety in children. These objectives must be achieved without undertaking unnecessary studies and without delaying the marketing authorisation of medicines for adults.

To comply with the Regulation, pharmaceutical companies need to submit a paediatric investigation plan (PIP) to the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) when developing a new medicinal product. The PIP must include all studies deemed necessary to demonstrate efficacy and safety for a claimed indication, and for all relevant paediatric age subpopulations, from newborns to adolescents. The Regulation also involves incentives for pharmaceutical companies. The latter are urged to complete studies included in the PIP irrespective of whether or not they ultimately obtain a paediatric marketing authorisation (MA) for the new medicinal product. Indeed, incentives are also granted when applicants fail to obtain marketing authorisation, due to the occurrence of significant adverse effects in children or lack of efficacy for example, since negative results from paediatric studies will be included in the summary of product characteristic (SmPC). These incentives take the form of a six-month extension to the supplementary protection certificate (SPC) of the new drug in all its indications, including in adults. A specific regulatory framework has also been established for drugs intended for orphan diseases or drugs that are no longer covered by a patent or supplementary protection certificate [2].

The ten-year assessment (2007—2016) of the European Paediatric Regulation was positive overall, with an unprecedented increase in the number of paediatric clinical drug trials [3]. In total, 276 new drugs were granted paediatric marketing authorisation during this period, 43 new dosage forms adapted to paediatric use were approved and approximately 950 PIPs had been validated by the PDCO [3,4]. However, the feedback also highlighted certain challenges in setting up and implementing PIPs [3,5—7].

Therefore, at the Giens Workshops 2022, a round table (RT) was dedicated to medicines in paediatrics and brought together public and private stakeholders and representatives of patient associations with knowledge on this subject. The group chose to address three priority topics in the field of paediatric drug development:

- optimisation of new drug development and feasibility of trials included in PIPs;
- management and restriction of persistent off-label prescriptions;
- development of new, adequate formulations in an ecosystem that favours innovation.

The RT members organised their work in four videoconference sessions. In each session, current data on a specific topic was presented by one of the participants, followed by a discussion. All proposals and conclusions were validated during a one-day, in-person meeting (end of June 2022). The synopsis of these discussions was presented in a plenary session, as with the other five RTs, at the end of the Giens Workshops 2022.

Optimising the development of new paediatric drugs

Observations

Paediatric patients are still excluded from clinical trials. In most diseases, the pathophysiological process, clinical presentation and therapeutic approaches are the same in both adults and children. However, the progressive development and maturation of physiological and cognitive functions during childhood (from birth to adulthood) may give rise to some nosological differences.

Since the European Paediatric Regulation came into force in 2017, the development of new medicines has been persistently driven by adult indications [3,7,8]. Waivers from conducting clinical trials are sought and granted for medicines that are not considered necessary in paediatrics, e.g., a new anti-cancer drug for lung cancer because the latter does not exist in children. These waivers are included in the PIP published on the EMA's website. However, the mechanism of action of the drug in question could potentially be of interest for treating a different type of cancer in children e.g. if the drug's target in lung cancer is also present in a paediatric cancer [9].

Similarly, PIP waivers may be granted in certain paediatric age categories — often in full-term and premature newborns. Indeed, few diseases in adults have an equivalent in neonatology yet, drugs marketed in adults are potentially useful for newborns. The current regulatory framework does not promote the development of new drugs for neonatal indications only [10,11].

Trials are insufficiently adapted to paediatric clinical practice and start too late compared to adult trials. It is often the case that the methodology of clinical trials in some PIPs is a simple copy of the adult development plan. However, the number of patients required for enrolment does not reflect the number of paediatric patients who are potentially eligible. Likewise, the complexity and number of proposed investigations do not reflect the reality of paediatric clinical practice [12,13]. Finally, paediatric trials are often started after completion of adult trials or even

after drug marketing authorisation has been obtained in adults, which often leads to off-label prescribing in children. Consequently, the feasibility of paediatric clinical trials is seriously compromised even before they get underway. Ultimately, this situation leads to numerous paediatric trials being postponed due to insufficient enrolment, and to extended delays in obtaining paediatric-use marketing authorisations [14].

The management of competing PIPs is difficult. The development of 'me-too' drugs to treat conditions that are common in adults but far less common in children has given rise to PIPs that are difficult to achieve [3,15]. This is even more the case as trials planned in these PIPs often start at the same time and result in multiple and uncoordinated solicitations of investigating clinicians by sponsors through Contract Research Organisations (CROs). All these procedures and solicitations increase the administrative burden of clinical trials and are generally counterproductive.

Recommendations

Given the current situation, the group underlines the importance of interactions between expert clinicians, representatives of patient/family associations and industrial and institutional stakeholders through existing networks at a national and especially, European level. These multi-stakeholder interactions will enable the undermentioned actions.

Define actual unmet needs in paediatrics and focus new drug research and development accordingly

Ahead of clinical development, the creation of strategy forums between partners from academia, industry, regulatory authorities and patient/family associations at a European or even international level will enable a more adapted and patient-focused definition of the unmet medical needs and the expected long-term benefits in each field of medicine. The expression and definition of these needs should also be supported through quantitative data from the field. These forums will also allow the prospective analysis (*horizon scanning*) of new molecules/drugs under development by industry and the dosage forms to be developed. Hence, the group underlines the importance of early consultations between industrial partners and health technology assessment (HTA) bodies in order to value specific innovations. These consultations will not take place at the strategy forums, but the decisions taken at the forums may influence the discussions during early consultations between industry and regulators.

Furthermore, scientific information sharing will increase the possibility of marketing new drugs based on their mechanism of action, not just their therapeutic indication. This has been the case with larotrectinib, for example, which targets certain solid tumours in children and adults with a specific genetic abnormality, regardless of tumour type [16]. Finally, the group emphasises the importance of family/patient associations' participation in these strategy forums. Their experience is paramount for defining medical needs, given that the ultimate goal of drug development is to treat and to improve the quality of life of children and by extension, that of their families.

The ''*Accelerate*'' initiative is a successful example of a multi-stakeholder strategy forum in the field of paediatric oncology [17]. The aim of this initiative is to identify unmet needs, evaluate and update scientific data through information sharing between partners, and guide future drug development strategies in paediatric oncology. Ten strategy forums have been held since 2017, supported by regulatory authorities in the EU (European Medicines Agency, EMA) and U.S. (Food and Drug Administration, FDA) that take part in the discussions [17—19]. More recently, strategy forums have also been organised through the European c4c network (conect4children, an IMI 2 Joint Undertaking project) [20] on paediatric inflammatory bowel disease (April 2021) [21] and atopic dermatitis (March 2022). The group recommends expanding this kind of initiative to cover all fields of paediatric medicine.

Although these forums will be created at the European or even international level, experts in France must be informed of these initiatives and encouraged to become actively involved. To achieve this, a national information and awareness policy must be set up in France for clinicians and patient/family associations through academic societies (*Société Française de Pédiatrie* - SFP [French Society of Paediatrics]; specialised academic associations, etc.) and national networks (Inserm PedStart network, F-CRIN; rare disease networks, etc.). To improve the training and involvement of expert clinicians, the group also recommends creating drug' working groups within all national academic paediatric associations; some of these groups already operate in certain clinical networks, notably the rare disease networks. The aim is to engage all paediatricians in the role of essential and active stakeholders in the development and evaluation of new drugs for children.

Overall, strategy multi-partner forums will help select and prioritise the development of innovative drugs, in keeping with patients' real needs and the latest scientific findings, and will improve coordination between partners, thereby restricting competitive and counter-productive clinical developments.

Determine necessary paediatric trials and their methodology prior to PIP submission

When the decision is taken to proceed with the clinical development of a new paediatric drug, it is essential to establish which studies should be included in the PIP. The group stresses the importance of using real world evidence (RWE) and the results of meta-analyses to:

- guide the decision on whether or not to extrapolate adult data to children [22];
- better apprehend the clinical context and the number of potentially eligible patients [23].

Furthermore, expert clinicians and researchers should validate reference methodologies and evaluation criteria for each medical field in paediatrics. This will considerably improve the conduct of paediatric trials and will enable scientific and regulatory requirements to better reflect the realities of clinical practice. To identify these experts, mapping of the different medical and paediatric clinical research

networks should be performed and regulatory authorities should be encouraged to involve external paediatric expertise through these networks.

Multi-stakeholder consultations to determine the type and methodology of studies included in a PIP will undoubtedly accelerate the conduct and implementation of these trials.

Optimise implementation and enrolment in PIP trials

The lack of paediatric expertise in the evaluation of applications submitted to regulatory authorities and ethics committees (ECs) causes considerable delays in obtaining the necessary authorisations and compromises future patient enrolment. Indeed, creation of ECs with specific ''mother-child'' expertise in France would be preferable. Also, initiation of trials is often delayed because of the overall administrative and logistical burden of clinical research and the absence of dedicated staff.

Therefore, the group recommends that academic and industrial sponsors make more widespread use of units specifically dedicated to paediatric clinical research, such as Clinical Investigation Centres (CICs) or Clinical Research Centres (CRCs), as well as associations of young patients. Indeed, several specialised facilities already exist in France and are organised in networks to improve communication and visibility. These include the F-CRIN-labelled Inserm PedStart network [24] or the KIDS France group [25]. The facilities involved in these networks have in-depth experience in managing interactions with the various French and European research partners, a standardised operating procedures and specially trained (medical and non-medical) staff. In addition, the group also recommends reinforcing interactions and collaborations between these specialised research facilities and the Reference Centres for Rare Diseases.

Finally, the logistical complexity of paediatric hospitals has an impact on trial participants and their families, especially when there are long distances between home and the healthcare facilities. Outpatient clinical research development and cooperation's between hospital and primary care research facilities is encouraged whenever possible. They should be considered based on the type of clinical trial, the pathology and the medicinal product in question, as well as the planned investigations. Vaccine trials are potential examples of trails that could be transferred to an urban setting [26].

The optimisation of paediatric trials in France presupposes the use of existing research facilities specialising in paediatrics. Yet, sustainability of these facilities depends on funding from academic and industrial partners that recognise the importance of clinical research in medicine. This kind of support will also help secure the human resources needed to map out the various facilities and specialised research networks in France.

Restricting off-label prescribing for paediatric use

Observations

Off-label prescribing remains common in paediatrics and concerns approximately 40% of drugs prescribed in paediatric intensive care and up to 80% of those prescribed in neonatology [27]. The group has identified two main types of off-label prescribing.

Prescription for indications not covered by the marketing authorisation. The European Paediatric Regulation allows applications for a paediatric marketing authorisation to be submitted for any drug on the market that is not covered by an SPC or by a patent but which is of therapeutic interest in paediatrics. This kind of marketing authorisation is known as a PUMA (paediatric use marketing authorisation) and applies solely to therapeutic indications intended for the paediatric population or sub-populations. It is granted for drugs with age-appropriate dosage, pharmaceutical form and route of administration [28]. The PUMA application is a voluntary process for the industrial partners and is accompanied by financial incentives. Nevertheless, this approach is not deemed attractive enough, since the number of PUMAs is currently extremely limited [3,4]. Only seven PUMAs have been obtained since 2006 [29]. The numerous difficulties encountered include a lack of actual valuing for developing dosage forms adapted for paediatric use, and a market limited to paediatric indications.

Prescription for dosages not covered by the MA. Drugs prescribed for the same therapeutic indication in both adults and children must have their doses adapted for children, especially for the youngest (under two years of age) [11,30]. However, industrial partners rarely sponsor or fund the pharmacokinetic studies needed to define appropriate paediatric dosing schemas. Moreover, academic investigators who launch this type of studies are often confronted with a lack of sufficient funding to carry them out and, above all, a particularly stringent legal framework (Jardé law) (authorisations, insurance, Patient Information Sheets, etc.) despite minimal risks and constraints for the enrolled children and an evaluation conducted within the framework of usual clinical management. As a result, the time required to obtain regulatory authorisations and to perform pharmacokinetic studies in children is particularly and unjustifiably, long.

Finally, the current regulatory framework of derogatory drug access authorisations, early access authorisations (EAA) and compassionate use authorisations (CUA) is unsatisfactory in paediatric medicine because it does not bind involved partners to engage in a specific clinical development or the follow-up of concerned children. It is important to note that in France, despite a wide portfolio of early access trials, 50% of children and adolescents with cancer who are refractory to previous treatments, receive a new drug outside the frame of a clinical trial, i.e., through compassionate or off-label use [31].

Recommendations

In response to the current challenges, the launch of specific French and European funding programmes and the development of public-private partnerships are strongly encouraged. These dedicated funds and partnerships are essential for performing:

- trials that may lead to the repositioning of drugs in paediatric indications. To that regard, the group emphasises the importance of significant and concrete valorising of drug repositioning and the recognition for innovations in the development of age-appropriate drug dosage forms. Such valorisations should exist regardless of whether the drug is developed for adult use, although the development of a new dosage forms could be of interest for certain adult populations, notably for the elderly [32,33];
- French and European pharmacokinetic trials for drugs frequently prescribed off-label in paediatrics. In addition, platforms must be created to centralise available paediatric pharmacokinetic data and enable meta-analyses. Such initiatives already exist in some European countries, such as the Netherlands (Dutch Paediatric Formulary) [34,35] and should be generalised;
- pharmacoepidemiological studies on the follow-up of children and adolescents who benefit from derogatory drug access (EAA, CUA) and/or off-label prescriptions. Indeed, it is essential to encourage these real-life studies based on healthcare, claims and/or hospital data, and on data collected from patient or specific drug user registers. These studies also contribute to the post-marketing follow-up that is increasingly required following the granting of a paediatric MA [3,36]. One example of observational data collection after granting of derogatory access, off-label and post-marketing drug use is the SACHA initiative in the field of paediatric haemato-oncology [32]. This study was initiated because a significant proportion of paediatric patients were not included in ongoing clinical trials or treated by drugs with a paediatric MA, and aimed to compensate for the loss of knowledge resulting from such uses. The assessment of safety and efficacy data for drugs prescribed under these conditions is prospective and data are collected on a national level in France. SACHA is a study launched by the French Society for Childhood and Adolescent Cancer and Leukaemia (SFCE), piloted and sponsored by the Gustave Roussy Institute in collaboration with the ANSM (French National Agency for the Safety of Medicines and Health Products) [37]. This kind of initiatives should be extended to other paediatric fields of medicine.

Lastly, it is important to underline the need for paediatric expertise in the evaluation of PIPs submitted to regulatory authorities and ethics committees in France. At present, the creation of ECs with a specific 'mother-child' expertise seems to be the only way to ensure that the current regulations (Jardé law) is applied while taking into consideration the specificities of studies with minimal constraints and risks in paediatrics.

Accelerate the development of dosage forms adapted for paediatric use

Observations

The need for adequate oral dosage forms is still not covered. The European Paediatric Regulation demands that the efficacy and safety of new paediatric drugs be evaluated in all age groups, from newborns to adolescents. However, the first step in this evaluation is the development of suitable dosage forms, particularly for the youngest. Indeed, every medicine must be administered orally in a dosage form that meets the following requirements [38—42]:

- it must be effective and easy to use and administer (liquid formulations are recommended for children under eight years of age). For the youngest patients, the drug must also be easy for the caregiver or family to use; for older children, the dosage form must ensure adherence to the treatment;
- it must allow for adapting doses;
- its concentration or dose must be suitable for the amounts to be administered;
- it must allow for a limited number of daily administrations (1 to 2);
- it must be risk-free, i.e. not contain any excipients that are potentially dangerous, particularly to newborns or in the case of long-term use;
- it must have an acceptable taste.

While the design of an adequate dosage form is mandatory for any new medicinal product within the framework of a PIP, for established, off-patent drugs, in most cases the available dosage forms do not satisfy the aforementioned requirements. Hence, the adult formulation needs to be modified to allow adapting of doses for an administration to children [38]. These practices lead to:

- dosing errors that result in lack of efficacy (under-dosing) or, conversely, in occurrence of adverse effects (overdosing);
- non-adherence to treatment [43—47].

The development of a new dosage form is time-consuming and not sufficiently valorised. A large number of PIPs reports were requested because of difficulties in developing an adequate paediatric dosage form, delaying the conduct of clinical trials and the obtaining of a paediatric MA. A minimum of five years is required to meet all the above requirements and succeed in achieving a marketed drug without taking in account challenges related to the choice of excipients or drug stability, for instance, that could further delay the process (Fig. 1). Also, to finalise technical development, a bioequivalence study with pharmacokinetic endpoints, most often conducted in adults, is necessary in order to obtain hybrid generic status, with some exceptions (BCS Class 1 drugs, etc.) [48]. To encourage these developments, the European Paediatric Regulation provides for incentives in the form of a six-month extension to the SPC or ten years of data protection for paediatric MAs (PUMA

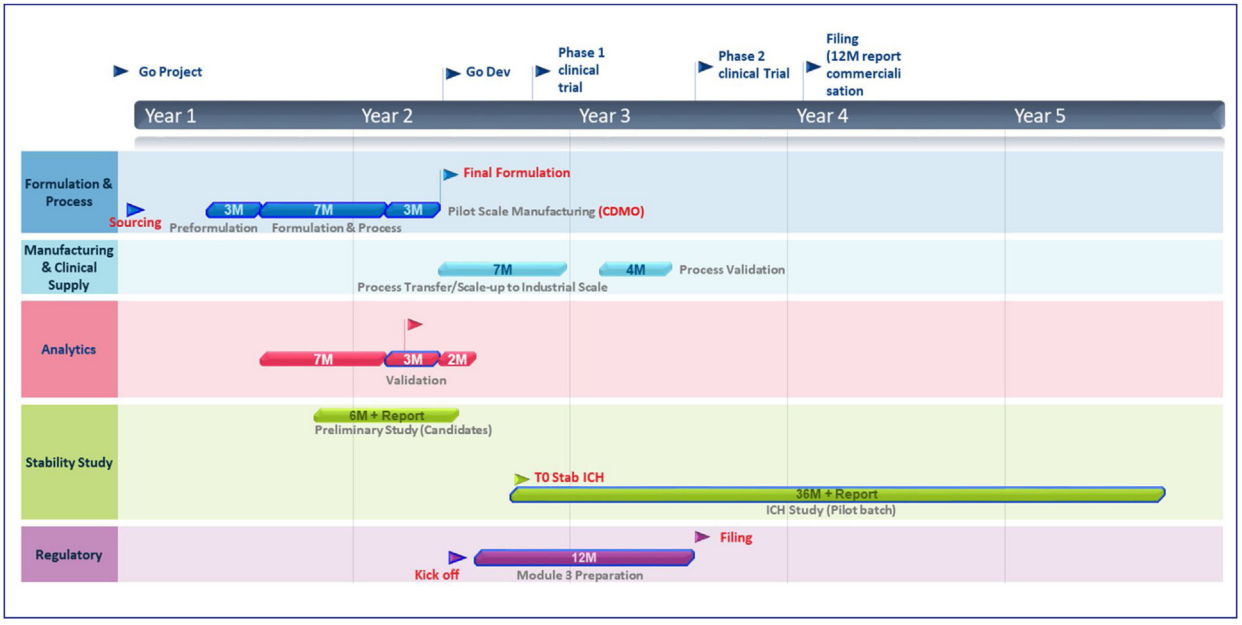

Figure 1. Time line for the new formulation of a medicinal product.

framework). To date, these incentives seem unsatisfactory in view of the costs incurred by the required technical development.

Recommendations

In light of this, the group has issued the undermentioned recommendations.

Give preference to new, solid dosage forms

Although liquid oral forms have long been deemed the gold standard of the appropriate paediatric formulation, their development has proven more difficult than initially expected. The high cost of their technical development, the difficulties in choosing excipients and the optimum concentration (allowing appropriate dosing in all ages) and their limited acceptability (taste issues) in children are just some of the issues encountered. However, given recent technological developments, other dosage forms may be better suited for paediatric use, such as mini-tablets, and orodispersible tablets and films (Fig. 2). These new, solid oral forms have two major advantages: firstly, taste masking, which is easier when the form remains solid; secondly, better stability and therefore, lower manufacturing costs. Moreover, mini-tablets less than 2 mm in size are suitable for administration starting at six months of age, while orodispersible films can be taken either intact or dissolved starting at six months of age [49—52]. The advantages and disadvantages of the different dosage forms for paediatric use are presented in Table 1.

Develop personalised medicine in terms of dosage forms and doses adapted to the target population

The emergence of these new solid forms also enables increasing personalisation of patient treatment, with doses and forms adapted to each patient. Indeed, fine-tuning of doses might be necessary in certain chronic pathologies (cancer, metabolic disease, etc.) or in some paediatric subpopulations (e.g. full-term or premature newborns). New technologies have recently emerged, such as 2D or 3D printing, which enable the production of customised doses for a patient from a ''cartridge'' [53]. These technologies also enable the creation of ''polypills'', combining several active substances in a single intake [54]. These technologies are gradually being introduced in European hospital pharmacies, and will enable personalised patient treatment in future by allowing dosage customisation through oral route.

Currently, these new technologies are used for dose customisation of established/marketed drugs and have yet to be proven through specific studies. Nonetheless, they are definitely opening the door to new manufacturing channels that are extremely promising and of interest both for patients and for pharmaceutical industry investments.

Establish an ecosystem that recognises the value of innovations involving adapted dosage forms

For both new and marketed drugs, the group highlights the need for a clearer commitment from the behalf of regulatory authorities regarding funding of paediatric dosage forms. The lack of visibility on the potential valorisation of innovation has a significant impact on private stakeholders' commitment to developing dosage forms for paediatric use. Potential levers could be the aforementioned early consultations between industry partners and Health Technology Assessment (HTA) bodies. Furthermore, in France, another option would be to re-evaluate the improvement of the actual medical benefit (ASMR, *amélioration du service médical rendu*) which determines drug commercial value. Finally, investment in new pharmacopoeia technologies can also be leveraged through their wider use, beyond the paediatric

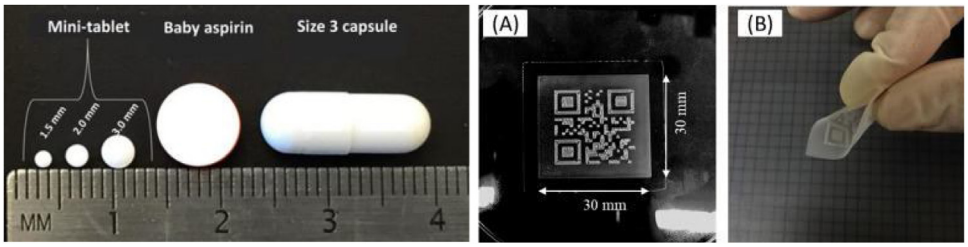

Figure 2. Illustrations of mini-tablets and orodispersible films.

Table 1 Advantages and disadvantages of dosage forms used in paediatric medicine.

Dosage form	Advantages	Disadvantages
Tablets or capsules	Well tolerated Effective taste masking Modified release formulation possible	Often too large Not suitable for adapted doses Often crushed in paediatric use
Mini-tablets/granules	Dose flexibility Well tolerated in young children	Administration device Number of tablets or granules to take per dose Manufacturing process can be complex
Orodispersible tablets	Well tolerated by all ages	Taste Sodium intake
Gummies, chewing sweets	Well tolerated	Not advisable under 2 years of age Less stable Cost of industrial production
Dispersible and orodispersible films	Tolerated starting at 6 months of age	Low doses; dose adaptation is complicated
Liquid form	Can even be used in newborns Adaptable dosage	Often tastes bad Stability problem Suspension has to be reconstituted Moderate ease of handling

population. In fact, innovation in drug dosage forms could be beneficial for other age groups such as the elderly who are also concerned by drug administration and adherence issues.

Conclusion

The regulatory initiatives of the last 20 years have resulted in unprecedented momentum in terms of the availability of new paediatric drugs. Yet, improvements are still required to ensure that paediatric drug research and development are truly based on real medical needs and current state of scientific knowledge. To achieve this, the synergic interactions between academic, regulatory and industrial stakeholders and patient/family associations must be strengthened by launching strategy forums in all paediatric medical fields. These interactions can also be optimised via existing academic societies and paediatric research facilities/networks at the French and European level. Finally, the development of new dosage forms and dosage customisation technologies, along with a greater recognition of related innovation, are potential levers for investment in the field of paediatric medicines. The recommendations of this RT proceed the revision of the European Paediatric Regulation on paediatric medicines and orphan diseases planned for January 2023.

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The other authors declare that they have no competing interest.

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