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Review Article

Theme: Pediatric Drug Development and Dosage Form Design
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Paediatric Drug Development and Formulation Design—a European Perspective

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Abstract. The availability of licensed paediatric drugs is lagging behind those for adults, and there is a lack of safe formulations in suitable doses that children are able and willing to take. As a consequence, children are commonly treated with off-label or unlicensed drugs. As off-label and unlicensed drug use are associated with a greater risk for harm than on-label drug use, a range of global initiatives have been developed to realize "better" medicines for children. This review describes the challenges and achievements of the European Union to realize this goal, with a focus on paediatric drug development and formulation design. In 2007, a European Paediatric Regulation was installed enforcing companies to consider children in the early development of drugs with a new drug substance, for a new indication or with a new route of administration. The Regulation, e.g. requires companies to develop a paediatric investigation plan discussing the proposed clinical trials in children of different ages and the formulations for future marketing. Since 2013, the pharmaceutical design of any newly marketed paediatric drug should comply with the "Guideline on the Pharmaceutical Development of Medicines for Paediatric Use." Companies should, e.g. justify the route of administration, dosage form, formulation characteristics, safety of excipients, dosing frequency, container closure system, administration device, patient acceptability and user information. In this review, the guideline's key aspects are discussed with a focus on novel formulations such as mini-tablets and orodispersible films, excipients with a potential risk for harm such as azo dyes and adequate user instructions.

KEYWORDS: child; EMA; formulation; guideline; pharmaceutical; technology.

INTRODUCTION

Worldwide, the availability of licensed, paediatric drugs is lagging behind those for adults, and the younger the child, the fewer drugs available (1–3). Even if a drug is licensed for paediatric use, it may not be suitable to administer all of the necessary (lower) doses, it may not be suitable for administering the drug to young children, or they may be poorly accepted (1). Thus, health care professionals are often left with no other option than to prescribe drugs outside the approved conditions for age, indication, dose, dosing frequency and/or duration of use (i.e. off-label use); to recommend an unapproved modification of a drug product such as crumbling tablets and mixing these with food or drink (i.e. off-label use) or to compound a drug product in the pharmacy from a mixture of the drug substance and suitable excipients (i.e. unlicensed drug use) (4, 5). However, off-label and unlicensed drug use are normally not supported by the same level of clinical and pre-clinical evidence as drugs that are used within their approved label conditions. As a consequence, off-label and unlicensed drug use may result in altered efficacy rates and an increased risk for harm and hospitalization (6).

It is evident that market forces alone have proven to be insufficient in ensuring the availability of licensed and age-

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appropriate drugs for children of different ages. This review describes the challenges and achievements within the European Union to improve paediatric drug development and the drug product (formulation) design.

Better Medicines for Children

In 2007, a European Paediatric Regulation (EC No. 1901/2006) came into force to realize better medicines for the children of Europe (7). The Regulation was based on lessons learned from earlier incentives by the US government which ultimately resulted in the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) (8). The Regulation has already been described elsewhere (9–11). In summary, it requires companies to consider children at an early phase in the development of a drug containing a new drug substance, intended for use in a new indication or administered via a new route of administration, unless a waiver applies. In order to fulfil this requirement, companies are obliged to develop a Paediatric Investigation Plan (PIP) including proposals for the clinical trials in children of different ages, the dosing recommendations, the formulations for each of the target age groups and the timelines for drug development. The PIP is subject to agreement by the European Medicines Agency (EMA) Paediatric Committee (PDCO). When new evidence indicates that the proposals in the agreed PIP are no longer adequate, companies should seek consent from the PDCO for a modification of the PIP. In order to ensure that the PIP is not just a plan, but also really followed during paediatric drug development, companies can only apply for drug approval at the EMA or any of the European national drug regulatory authorities when compliance to the PIP has been confirmed.

Acknowledging that information on the pharmaceutical design of paediatric drugs in relation to patient outcomes was scarce and fragmented, the Paediatric Regulation has triggered a variety of research opportunities (12, 13). In addition, several research consortia were established, e.g. European Paediatric Formulation Initiative (EuPFI), Global Research In Paediatrics network of excellence (GRIP) and European Study of Neonatal Excipient Exposure (ESNEE) (14–16). Furthermore, the EMA set up a European Network of Paediatric Research (Enpr-EMA) to assist stakeholders in paediatric clinical studies by bringing together research networks, investigators and centres with recognized expertise in this domain (17). Besides research, the Regulation has also promoted the (further) development and harmonization of national paediatric formularies such as the British National Formulary for Children and the Dutch Paediatric Formulary (18, 19). In due course, these will be supplemented by a harmonized pan European Paediatric Formulary, which is currently being developed by the European Directorate for the Quality of Medicines & HealthCare (EDQM) (20).

Paediatric Drug Development: Dosing Aspects

Human growth is not a linear process. As such, children are not small adults, and paediatric doses cannot be calculated (extrapolated) as a standardized fraction of the dose for adults. Rather, the development and use of paediatric drugs requires specific knowledge on the age-related aspects of the drug's absorption, distribution, metabolism and elimination characteristics, i.e. pharmacokinetics (PK), as well as its receptor and organ interaction, i.e. pharmacodynamics (PD) (21). Moreover, it must be realized that the permeability and solubility of a drug substance in children may differ from adults, meaning that the Biopharmaceutical Classification System (BCS) must be used with caution (22, 23). When deciding on suitable dosing, other aspects which may have an impact on the PKPD of a drug product in an individual child must be considered as well, e.g. genetic variability (24, 25), maturity of enzymatic systems involved in metabolism (26), concomitant drug use and co-existing diseases (27, 28), hypothermic treatment procedures (29, 30), obesity (31).

Accurate dosing can only be assured when the pharmaceutical design of the drug product includes the recommended dose or allows this dose to be measured correctly, when the child is able and willing to use the drug product as intended and when the child's caregiver is able and willing to administer the dose correctly and as recommended (32–34). Moreover, a flexible dosage form is required when minor changes in age, body weight and/or body surface result in different dosing recommendations (33).

Paediatric Drug Development: EMA Guidance on Drug Product Design

Background

The European Paediatric Regulation was supported by an EMA reflection paper on "Formulations of choice for the paediatric population" describing the issues to be considered in the pharmaceutical design of drugs for paediatric use (35). Being a reflection paper, the document was intended to "communicate the current status of discussions and to invite comments to the topics addressed, rather than to provide scientific, technical or regulatory guidance" (36). Yet, the reflection paper was nevertheless used as such. Therefore, in 2008, the drafting of an actual guideline was initiated by the publication of a concept paper (32). In order to enable early dissemination of guidance on the topics addressed, the concept paper was supplemented with an annex stipulating the basic guidance principles (32). The guideline itself was adopted in 2013 together with an overview of the stakeholders' comments to the draft versions and the way these had been addressed. As can be read from these overviews, the guideline may be supplemented in due time with Question and Answer (Q&As) documents reflecting new scientific evidence (37, 38).

Scope

Drug users may expect that similar drug products will have similar quality standards regardless of the trademarks dispensed. For example, that all tablets with a line suggesting breaking will actually break into equal fragments, or that all amoxicillin suspensions are well palatable. Acknowledging a wide variety in patient expectations, patient-reported problems and medication errors related to paediatric drug design, it was decided that the guideline should apply across all the European drug licensing procedures (centralized, decentralized, mutual recognition, national) and for any new application, whereas the principles may also be considered for the PIPs. Moreover, companies were clearly reminded about

their legal obligation "*to re-evaluate the usefulness (practicality), quality, safety and efficacy of drug products over time, and, where appropriate, adapt or improve the design of the drug product in the interest of the drug users and to maintain a positive benefit to risk profile*" (33). As the guideline was adopted 6 years after the Regulation had entered into force, it must be acknowledged that some earlier PIPs may reflect other views than those presented in the guideline.

In order to avoid repetition of data, the guideline is limited to those aspects of paediatric drug design that differ between children and adults or at least require further justification. Thus, the guideline should be used in connection with all other European regulatory provisions such as the EMA and "International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use" (ICH) quality guidelines and the European Pharmacopoeia (Ph. Eur.). Consequently, the paediatric guideline does not provide an exhaustive list of all aspects to be considered in paediatric drug design. In Table I, the authors have prepared a list of issues that may be considered.

Scientific Content

The scientific content of the EMA paediatric guideline is divided in sections relating to the route of administration and type of dosage form (formulation), excipients in the formulation, dosing frequency, fixed dose and modified release drug products, container closure systems, administration and measuring devices, patient acceptability and the user instructions in the product information, i.e. in the Summary of Product Characteristics (SmPC), Package Leaflet (PL) and/or on the product label (33).

The guideline indicates that any drug should be designed to meet patient needs and consistently deliver the intended product performance (33). In accordance with the ICH Q8 guideline on "Pharmaceutical development," a systematic approach to the pharmaceutical drug design is envisaged including a definition of the drug quality target product profile (QTPP) and identification of the product critical quality attributes (CQAs) (33, 64). It is evident that a drug may often need to be marketed in a range of strengths and possibly several types of dosage forms. In exceptional cases, drug products may include different forms of the active moiety to enable the manufacture of a specific type of dosage form, e.g. the salt form rather than the base to ensure that the active substance dissolves into a solution (33).

Route of Administration, Dosage Form, Formulation

General Considerations

For generations, it was considered that young children would best be treated with oral liquid formulations, as these were easy to swallow and would provide adequate dosing flexibility (65). However, the use of oral liquids may be associated with numerous problems, including bad taste, limited chemical, physical and/or microbial stability, need for a dosing device, risk of errors when measuring the dose, sedimentation and inhomogeneous distribution of the drug substance, emulsion splitting, bulky volumes and portability issues. Most of these problems may be avoided by conventional oral flexible solid paediatric formulations such as powders or granules; however, these may be badly accepted. Therefore, newer oral flexible dosage forms such as mini-tablets or oro-dispersible films may be more appropriate (66). Novel approaches such as the oral solid dosage pen, where the dose is adjusted by cutting a tablet-like drug carrier at a pre-defined height, are expected to introduce further flexibility and convenience to paediatric dosing approaches (67).

Mini-Tablets

The EMA paediatric guideline states that small tablets (also referred to as mini-tablets) may be considered as a measure to improve acceptability and dosing flexibility in children, as several tablets can be taken as a single dose (33). However, it does not specify when tablets are to be considered as small, although a limit up to 5 mm has been proposed in the draft for public consultation (Fig. 1) (37). The guideline clearly indicates that, apart from size and shape, the suitability of small tablets should also be justified in relation to child health conditions, disease development and the risks associated with chewing, choking, aspiration and over- and under-dosing (33).

The acceptability of oral formulations in young children, e.g. mini-tablets, has already been discussed elsewhere. In summary, we have found that 4-mm uncoated mini-tablets can be used successfully in children from 1 year of age (46). In addition, Klingmann et al. showed that smaller 2-mm mini-tablets can be used in infants from 6 months of age, whereas 2 mm rapidly dissolving mini-tablets can be used as early as in the pre-term age (47, 48). These studies actually indicated that mini-tablets are equally or even better accepted than oral

Table I. Aspects to be Considered in a Holistic Approach to Pharmaceutical Drug Product Design

1. Disease characteristics, e.g. need for incidental, intermittent or chronic drug use and duration of therapy (39); need for different routes of administration (40); impact of the disease on child cognition and behaviour (41); risk for co-morbidities (42, 43);
2. Variability of children within the target age group, e.g. age (1, 44), weight (30, 44), surface area (45) and body composition (30, 44);
3. Characteristics of the individual child, e.g. ability and willingness to swallow a specific drug product (46–51), multiple medication use or polypharmacy (27, 44), disease progression (39, 44);
4. Characteristics of the drug substance, e.g. pharmacokinetics (PK), pharmacodynamics (PD) (44), minimum and maximum dose per target age group and need for small dosing increments (51); minimum and maximum dosing frequency (41); volume of water necessary to dissolve and swallow the dose (52), impact of oxygen, vapour and higher temperatures on degradation and risk for drug-drug interactions (26, 27);
5. Characteristics of the drug product, e.g. feasibility of the manufacturing process (45), need for inclusion of certain excipients in specific types of dosage forms and the safety of such excipients (44, 53), taste (54, 55), need for dosing and other medical devices (33), need for product handling (56), risk for medication errors (51, 57);
6. Parents' beliefs, attitudes, convenience and opinions (58, 59), setting where the drug product will need to be administered (52), culture (60);
7. Patient access, e.g. cost (61), reimbursement (51), regulatory challenges (62, 63).

Fig. 1. Volume and size indication of 250 mg oral powder, 2-mm tablet, several 2-mm tablets and 4-mm tablet on plastic spoon for infant use

syrups. Moreover, Kluk et al. confirmed that mini-tablets can be used as a flexible dosage form since children from 2 years of age were able to take 5 to 10 tablets in a fruity jelly on a spoon (49). Although the co-administration of medicines with food or drink is a common practice in children, concerns have been raised on the possible impact of the food or drink upon direct contact with the drug product. The concerns mainly relate to the possible effect on physical parameters such as the particle size or tablet coating or on the release of the active substance from the drug product, i.e. the drug product bio-availability (65, 68).

The aforementioned studies on mini-tablets were conducted in three European countries only (Germany, Poland, Netherlands). Therefore, it cannot yet be excluded that cultural differences influenced child acceptability. At the same time, it must be acknowledged that the age at which a mini-tablet can be taken may depend on the fact as to whether it must be swallowed intact, whether it may also be chewed, the presence of coatings and the time to dispersion or dissolution. In this respect, it must be reminded that the guideline clearly indicates that immediate release tablets are normally intended to be swallowed intact but that they may also be chewed unless otherwise indicated (33). An overview of current evidence supporting the use of mini-tablets in children of different ages is published by Liu et al. (69). Further evidence may be obtained from studies where the use of mini-tablets was not explicitly reported (58).

Orodispersible Films

Orodispersible films are single- or multiple-layer thin polymer sheets that are intended to be placed in the mouth where they usually disperse rapidly before being swallowed. They are not explicitly discussed in the EMA paediatric guideline, but their suitability for paediatric drug therapy is increasingly discussed in the scientific literature (70, 71). The main advantages of orodispersible films include easy administration, easy dose measurement, limited risk for spillage, no risk for choking and the possibility to cut the film in different sizes during product manufacture (dosing flexibility). However, patient acceptability, product mechanical strength, product packaging and the risk for medication errors associated with the use of this dosage form require particular attention. For example, the film colour should not trigger abuse and aspects such as the product taste, film texture and mouthfeel should remain acceptable following the wetting of the film in the mouth. Moreover, the pH at the product-mucosal interface should not cause irritation and/or pain. Other disadvantages of orodispersible films include limited load of the drug substance, higher production costs in comparison to conventional tablets and capsules and the lack of a harmonized test methods and regulatory provisions (70).

Excipients

Excipients may serve specific purposes, e.g. diluent, preservative, colouring agent, coating. According to the ICH Q8 guideline, the excipients chosen, their concentration, and the attributes relevant to their function in the drug product should be justified. However, excipients that are commonly used in drugs for adults may not be equally safe when used in children, even when used in proportional (lower) concentrations (64). Nevertheless, excipients with a potential cause for concern may be essential to the development of a specific dosage form. Therefore, the EMA paediatric guideline includes a detailed list of points to consider in the evaluation of the safety profile of excipients. Justification can, e.g. be based on their inclusion in marketed drug products when certain criteria are fulfilled or any relevant opinion of the European Food Safety Agency (EFSA). Only in exceptional cases, additional data such as (juvenile) animal studies, pharmacokinetic data or clinical studies may be necessary

(33). However, in all cases, it must be realized that the use of a potentially harmful excipient might be avoided by selecting another route of administration, other type of dosage form, etc. (33).

Current Experiences

A 5-years evaluation of the formulations in the PIPs revealed that many questions had been raised to the excipient composition (72). Following a detailed analysis, we concluded that the PDCO evaluation had resulted in little changes to the company's proposal. Apparently, companies had been able to adequately answer the EMA questions (73). Acknowledging that industry would benefit from readily available and up-to-date information on the safety of excipients in children, the EuPFI has established a freely accessible Safety and Toxicity of Excipients for Paediatrics (STEP) database (53). The consortium has also contributed to valuable excipient reviews, e.g. by Walsh et al. (54).

Considering that it is relatively easy to implement changes in the pharmaceutical design of a paediatric drug product during the early phases of drug development, it is not yet clear to which extent a precautionary approach to the excipient composition should be envisaged in the PIPs. For example, if the proposed formulation in the PIP would include wheat starch (which may cause problems in some children with coeliac disease) or lactose (which may cause problems in some children with lactose intolerance), would this formulation be acceptable, or should the company be asked to replace these excipients with other excipients serving the same function? And what if the formulation in the PIP includes excipients which may cause problems in children with less common deficiencies, e.g. hereditary fructose/galactose intolerance? Some excipients are also known for their allergic potential in children, e.g. arachidis oil, sesame oil, soya oil. Again, the question arises whether formulations with such excipients could be accepted in the PIP. Increased discussion among regulators, industry and academia will help realizing a transparent and consistent approach on this dilemma for future applications.

Azo Dyes

In 2007, McCann et al. (University of Southampton) concluded that six colours that were common in food for children were associated with an increased risk for hyperactivity (74). These so-called "Southampton six" include Tartrazine (E102), Quinoline Yellow (E104), Sunset Yellow FCF (E110), Carmoisine (E122), Ponceau 4R (E124) and Allura Red (E129) (74). In 2008, the study was evaluated by the EFSA. They concluded that the study showed significant methodological shortcomings, that it was not possible to pinpoint which of the investigated substances had been responsible for which of the observed effects and that there was insufficient reason to change the daily acceptable intake of the azo dyes E110, E122, E124 and E129 (75). However, from 2009, a re-evaluation of the safety of colouring agents, including the Southampton six, has resulted in a reduction of the acceptable daily intake of E104, E110 and E124. At the same time, the use of the Southampton six is progressively decreasing in food for children on a voluntary basis (76).

The EMA paediatric guideline does not include any specific guidance on azo dyes, implying that the general points to consider apply. However, the 2007 "Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product" clearly indicates that azo dyes (and other synthetic colouring agents) should not be used in (new applications for) paediatric drug products (77). Some stakeholders consider that the 2007 excipients guideline should be strictly followed, others that the excipient guideline is overruled by the newer paediatric guideline and the EFSA opinion, which do not support a strict ban of azo dyes in paediatric drugs (75, 76). Certainly, public acceptance of azo dyes is lower in countries where voluntary removal of such dyes has occurred in foodstuffs. Therefore, a harmonized opinion on the acceptability of azo dyes in paediatric drugs should be envisaged.

A search in the Medicines Information Bank of the Medicines Evaluation Board in the Netherlands (MEB) on 27 January 2016 revealed that many drugs contain one or several of the Southampton six: Quinoline Yellow in 110 licensed drug products for paediatric and/or adult use, Sunset Yellow in 519 products, Carmoisine in 40 products, Ponceau 4R in 97 products, Allura Red in 27 products (78). A preliminary evaluation of the lists revealed that some products were actually developed for use in infants and preschool children. Although further evaluation would be necessary to determine the exact number of drug products which contain a specific azo dye per indication and target age group, the search results support a regulatory discussion on the acceptability of azo dyes in both newly applied as well as licensed paediatric drug products.

Excipient Labelling

The need for drug users (health care professionals, patients, caregivers) to obtain adequate information on the drug product excipient composition is commonly acknowledged. Therefore, all excipients contained in the drug product should be listed in the product information. In addition, for some excipients, the full quantitative information should be provided to evaluate the excipient burden per single and daily dose and in case of multiple medication use (79). In 2012, a multidisciplinary expert group has been established with a mandate to review the 2003 "Guideline on Excipients in the Label and Package Leaflet of Medicinal Products for Human Use" (79). This work has been undertaken to ensure the safe use of drugs containing excipients with a potential safety concern, e.g. alcohol. The work is still in progress, but the first recommendations can be found on the EMA website (80).

Paediatric Drug Product Design: Patient Acceptability

Adequate patient acceptability is key to drug efficacy and safety (33, 50, 54). According to the EMA paediatric guideline, patient acceptability is determined by the characteristics of the drug product and the user. Although the term is often considered equivalent to drug product taste and/or palatability, the guideline clearly indicates that other aspects may be of relevance, e.g. product appearance (size, shape, colour, coating, printing, embossing), package, type of dosing device.

The guideline indicates that, where possible, patient acceptability should be studied in children as part of the clinical programme, although it may also be studied through

other means, e.g. by review of literature references or by studies in trained adult panels (33). No guidance is given on the test method and acceptance criteria, implying that any properly justified proposal may be accepted (81). The guideline does not explicitly address *in vitro* measurements for taste assessments such as the electronic or e-tongue. Current evidence indicates that this method can be valuable to industry when evaluating the effect of taste masking techniques during product development (82). In due time, a harmonized opinion on the acceptability testing of paediatric drugs should be envisaged.

Paediatric Drug Product Design: User Instructions

Any benefit-risk evaluation of a drug product for use in any patient population is based on the assumption that the benefit is greatest and the harm is least when the drug is taken as intended. Therefore, the EMA paediatric guideline stipulates that the user instructions in the authorised product information are an integral part of the drug product design (33). Acknowledging that health literacy and information needs may differ among drug users and that package leaflets may get lost, some European regulatory agencies have a publicly available drug database where parents can both read the package leaflet as well as the SmPC of a specific drug product and where a free text search can be conducted in all the SmPCs and package leaflets that are included in the database (83).

In daily practice, it may not be feasible to use a drug product as intended, e.g. because of swallowing difficulties or recalcitrance. Therefore, children will benefit from adequate information on the intended as well as any alternative administration strategy in the product information (56). Some of such alternatives have been addressed in the paediatric guideline, e.g. tablet breaking, administration through a feeding tube or taking a drug product with food or drink (33).

Breaking

In Europe, break marks may be present to provide fractions of the full tablet dose or to ease swallowing (84). The EMA paediatric guideline clearly indicates that the function of the break mark should be stated in the product information, i.e. for the administration of lower doses or for ease of swallowing the full tablet. Where the break mark is intended for dose reductions, the suitability of the break mark should be justified. This implies that the tablets should comply with the Ph. Eur. test on the "uniformity of mass of subdivided tablets." Acknowledging that scientific evidence had indicated that breaking may not be accurate in clinical practice, the guideline also indicates that break marks for paediatric dosing may not be accepted in case of potent active substances with a narrow therapeutic window. The guideline does not address the use of tablet splitters which have generally proven to be less accurate than breaking tablets by hand but rather states that justification of the suitability of the break mark includes the ease of breaking (33, 84).

Feeding Tubes

Children who are premature, seriously ill or who are otherwise unable to take the necessary calories by mouth may be nourished through a feeding tube. In such cases, the tubes are also commonly used to administer oral drugs (85). The guideline states that where administration through a feeding tube is highly likely, the product information should indicate if such administration route is possible and which procedures are to be adopted. When justifying this route of administration, aspects to be considered include those related to tube blockage such as particle size and viscosity or to accurate dosing such as drug adsorption to the tube material, rinse volumes and dose recovery after extrusion. In addition, the risk of accidental aspiration and the potential impact on bioavailability should be discussed (33).

Administration with Food or Drink

Unless otherwise justified, drugs should be well accepted and thus sufficiently palatable in children of different ages when taken on their own or with some water only (33). However, it is not realistic to expect that every child will accept a well-developed oral drug formulation, as the child's state of mind (behaviour) and individual preferences may play a role (33). Therefore, the EMA guideline clearly acknowledges that the lack of any recommendation on the co-administration or mixing of drugs with food or drink does not imply that drug users will avoid this method of administration. Thus, the guideline requires that companies should undertake the necessary studies and discuss the joint intake of the drug product with common foods or drinks in the development pharmaceutics. In case of relevant interactions, companies should include a clear warning in the product information (33).

In-Use Shelf-Lives

The EMA guideline on "declaration of storage conditions" describes that companies should study, or otherwise justify, the shelf-life of drug products after opening of a multi-dose container. When it cannot be excluded that opening affects the drug product stability in the licensed container, an in-use shelf-life should be included in the product information. When the data indicate that opening does not have an impact on the drug product stability, no information on the in-use shelf-life is foreseen.

Some European authorities consider that additional measures may be necessary to further improve the safe and correct use of the drug products on their market. For example, it is known that ADHD patients may use multiple compartment aids to favour medication management and ensure adequate drug adherence. Recently, an increase of tablet cracking was observed for methylphenidate extended release tablets, possibly because the tablets were stored outside their licensed container in e.g. a multicompartment compliance aid. On request of many stakeholders, the problem was solved by the company on short time by changing the tablet coating. At the same time, the MEB agreed that the product information could be supplemented with information on the period the tablets could be stored outside their primary container (86).

Paediatric Regulation: Progress and Future Perspectives

Following 5 years of experience, the EMA concluded that the Paediatric Regulation was a success, e.g. because drugs were increasingly being studied in children of younger ages and because the formulation proposals had prompted discussion with companies on many issues (72). However, the value of some paediatric trials is disputed by some stakeholders arguing that different companies were obliged to conduct similar studies in small patient populations (62). Moreover, there are uncertainties on the effectiveness of the Regulation to reduce off-label and unlicensed paediatric prescription rates as many essential and common drugs have been licensed before the Regulation entered into force. For example, Lindell-Osuagwu et al. compared off-label and unlicensed prescription rates in several paediatric wards in a Finnish university hospital. They actually found that off-label use and unlicensed drug use was more prevalent in 2011 than in 2001 (87). Also, on the basis of 117,665 admissions over 1 year in a French paediatric hospital, Lajoinie et al. concluded that young children are still commonly treated with unlicensed drugs (88).

All these observations support the need for close collaboration between regulators, drug developers, hospital pharmacists and clinical practitioners to evaluate the real benefit of the Regulation and to propose any adaptations in the interest of children. In addition, the need to carefully consider patients as active collaborators rather than subjects is increasingly acknowledged (89). Acknowledging the limited number of paediatric use marketing authorisations (PUMAs), it is commonly agreed that the Regulation may need to be changed in order to promote paediatric trials in off-patent drugs, whereas other limitations have been observed as well. Some adaptations have already been implemented (90).

It may be highly questioned if companies have sufficiently taken their responsibility to improve the design of licensed paediatric drugs up to the standard outlined in the guideline. When existing problems prevail, stronger measures may be considered to ensure that children will have access to age-appropriate drugs, regardless of the date at which the drug products were licensed. At the same time, it may be considered that other populations may have similar needs as children, e.g. older people (40). Rather than focussing on a gold standard paediatric drugs, companies may consider the development of patient centric products that can be used to accommodate certain patient needs across a wide variety of ages (69).

CONCLUSION

The European Paediatric Regulation has successfully focussed its attention on the pharmaceutical design of paediatric drugs. New(er) types of dosage forms, such as mini-tablets or oro-dispersible films, are increasingly being developed, and information on the safety of excipients is more readily available. An EMA paediatric reflection paper and guideline have been published to assist industry in the development of licensed and age-appropriate paediatric drug products. The guidance goes beyond formulation issues and also addresses other topics, such as patient acceptability and drug product usability in clinical practice. The guideline also stipulates the importance of understandable information for patients and caregivers in order to increase patient acceptability and adequate drug handling. However, further research in some areas of paediatric drug development is required in order to assure that paediatric drugs are age-appropriate and of the required standards, e.g. safety of excipients, acceptability testing. Progress can be achieved through closer collaboration of pharmaceutical companies, regulators, academia, practitioners, patients (children, parents and other caregivers).

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