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PEDIATRIC DOSAGE FORM -CHALLENGE FOR PHARMACEUTICAL INDUSTRY

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ABSTRACT

Despite the fact that a significant percentage of the population is unable to swallow tablets and capsules, these dosage forms continue to be the default standard. These oral formulations fail many patients, especially children, because of large tablet or capsule size, poor palatability, and lack of correct dosage strength. The clinical result is often lack of adherence, and therapeutic failure. The lack of an appropriate dosage form limits the use of many medications that may potentially benefit children. While this has been a long-standing problem for pediatric healthcare providers, little attention has been paid to remedying it until recently. This review gives an overview of the limitation of pediatric dosage forms, regulatory aspects for pediatric drug development, challenges in the development of pediatric dosage forms, excipients in the pediatric formulation and their influence on practical and scientific considerations when conducting clinical studies in children.

Key words: Pediatric, Regulatory aspects, Palatability, Excipients.

INTRODUCTION

The lack of an appropriate dosage form limits the use of many medications that may potentially benefit children. While this has been a long-standing problem for pediatric healthcare providers, little attention has been paid to remedying it until recently [1].

Children's medications can be a challenge for physicians and pharmacists. Because most marketed drugs do not have U.S. Food and Drug Administration (FDA)-approved indications for pediatric use, physicians must prescribe them "off label." When drugs do not have labeled indications for children, drug manufacturers do not produce strengths and dosage forms appropriate for this patient population. Technological limitations are rarely the reason for the lack of pediatric formulations; rather, market conditions often dictate the types of drugs for which formulations suitable for children are made available [3, 5].

It has been well established that children are not small adults but rather a distinct and heterogeneous patient group with regard to pharmacotherapy. They often exhibit a different response to both active substance and excipient . Children present a continuum of growth and developmental phases as a result of their rapid growth, maturation of the body composition, and physiologic and cognitive changes during childhood [2].

Children differ from adults in many aspects of pharmacokinetics and pharmacodynamics, potential routes of administration, medicine-related toxicity, and taste preferences [6, 7].

Important pharmacokinetic differences between children and adults include the rate of gastric emptying and pH, gastrointestinal permeability, and the surface area available for drug absorption. Dissimilarities have also been reported in drug metabolism, transporter expression, biliary function, and renal clearance, resulting in differences in drug disposition and elimination [8,9].

The largest deviation from adult pharmacokinetics is observed in the first 12 to 18 months, when organ functions are developing. In older children and adolescents, the pharmacokinetic parameters approach adult values and are thus easier to predict. The effect of age on pharmacokinetics leads to different dosing requirements for different age groups. From birth to adulthood, the body size and weight of an average child increases up to 20-fold, and the magnitude of dose variation administered throughout childhood may be 100-fold. More dramatically, premature neonates admitted to the hospital can weigh as little as 500 g, further highlighting the need for dose variability. Maturation processes in children are not linear, and therefore doses in

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certain age subsets may be lower, identical to, or higher than in adults, depending on a drug's metabolic pathway [10,11].

Due to this extensive variability in children, there is an obvious need for drug formulations tailored to children in all the target age groups. The International Conference of Harmonisation divides childhood into 5 age groups related to the developmental stages, derived from the physiologic and pharmacokinetic differences mentioned earlier. These groups (with age ranges) are: preterm newborn infants; term newborn infants (0–27 days); infants and toddlers (1–23 months); children (2–11 years); and adolescents (12–16 years in the United States or 12–18 years in the European Union).

The European Committee for Medicinal Products for Human Use further subdivides the age group "children" (2–11 years) into "preschool children" (2–5 years), and "school children" (6–11 years) to more precisely reflect the children's ability to accept and use different dosage forms.5 However, the classification of the pediatric population into age categories is to some extent arbitrary because children of the same chronologic age may still develop at different rates [9].

LIMITATION OF CURRENT DOSAGE FORM

One of the greatest challenges in pediatric pharmacology has been optimization of oral drug delivery. Although most children over 6 years of age can be taught to swallow solid dosage forms, many remain uncomfortable with it until adolescence.Swallowing of oral solid dasage form is a basic problem associated with children up to six years[1].

- Crushing tablets to mix them with food or water may change the rate or extent of drug absorption.
- Cutting tablets, another common practice, may be acceptable for some drugs, however this practice can introduce considerable variability between doses. In drugs with a narrow therapeutic index, produces clinical variability.
- Solids are associated with the risk of choking or chewing and with limited dose flexibility [2].
- Commercially available oral liquid medications provide a more reliable, ready-to-use preparation for infants and children, but bioequivalence with solid oral dosage forms is still not assured.
- The traditional method of preparing liquid formulations of these drugs has been as alcohol based elixirs. The concentration of alcohol in elixirs varies from 5% to as much as 40%. The long-term effects of repeated exposure to the alcohol in these products, particularly in infants and toddlers, are not known.
- Palatability and dose uniformity may be challenging for liquid preparations. In addition, liquid forms raise issues regarding stability (chemical, physical, or microbiological) and the requirement for clean water; moreover, they can be bulky, impractical, and expensive to ship and store, particularly in lower income countries with hot and humid climates [2].
- Preparation of oral medicines for children is subject to much variation in U.S. hospitals, and there is little harmonization of formulations or information on the stability of preparations [3].
- The use of nonoral routes of drug administration may be hampered by difficult application, local irritation, fluid overload, electrolyte imbalance, or poor drug acceptability .In neonates, intravenous administration may lead to volume overload. Moreover, measuring small dose volumes may cause large dosage variations and errors [2].
- A major problem in treating sick newborns is the lack of appropriate concentrations of various drugs for parenteral administration [3].
- Alternative nonoral routes of administration include rectal, dermal, nasal, pulmonary, and ocular routes.The use of nonoral routes of drug administration may be hampered by difficult application, local irritation, fluid overload, electrolyte imbalance, or poor drug acceptability[2].
- In neonates, intravenous administration may lead to volume overload. Moreover, measuring small dose volumes may cause large dosage variations and errors [4].

REGULATORY ASPECTS OF PEDIATRIC DRUG DEVELOPMENT

Over the past decade, regulatory legislations for drug development in pediatric patients were passed worldwide, dramatically increasing the number of drugs tested in and labeled for children. Both, the Food and Drug Administration (FDA) in the United States (U.S.), and the European Medicines Agency (EMA) in the European Union (E.U.), established approaches that have been successful in generating important new information about the safety and efficacy of drugs used by children [12, 13].

Transparency and accountability of pediatric drug development has improved and the amount and quality of pediatric information was increased by an elevated number of clinical trials in children in recent years. The progress was achieved by combining requirements for pediatric drug development with incentives for the pharmaceutical industry to (at least partly) cover the additional investment for testing drugs in children. There was and still is effort needed to harmonize the regulatory framework for pediatric drug development, but as of today pharmaceutical companies are still facing the problem that the regulatory requirements differ between FDA and EMA and that the development of a new drug in the pediatric population has to be in line with requirements from both authorities. Enforced by the authorities—in particular the EMA—pediatric aspects have to be integrated early in the development process of a new drug and the general strategy has to be part of the overall development program.

U.S. perspective

Historically, only a small fraction of all marketed drugs have had clinical trials performed inpediatric patients and a majority of marketed drugs were not labeled for use in pediatric patients. Accordingly, many drugs were administered to children in an off-label fashion without adequate understanding of appropriate dose, safety, or efficacy. The first initiative took place in 1994 when the Pediatric Labeling Rule was issued requiring

drug manufacturers to survey existing data and to determine whether those data are sufficient to support additional pediatric use information in the drug's labeling. Under the Pediatric Labeling Rule, if a manufacturer determines that existing data permit modification of the label's pediatric use information, the manufacturer must submit a supplemental new drug application (NDA) to FDA seeking approval of the label change [14].

The Pediatric Labeling Rule allowed the labeling of drugs for pediatric use based on extrapolation of efficacy in the adult population and additional pharmacokinetics, pharmacodynamics, and safety studies in pediatric patients, but only if the course of the disease and the response to the drug were known to be similar in children compared to adults.

Although this rule was designed to improve pediatric labeling, only a small number of well-designed and well-conducted studies subsequently resulted.

Since the approach under the Pediatric Labeling Rule was entirely voluntary, and did not substantially increase the number of products with adequate pediatric labeling, the FDA proposed (1997) and finalized (1998) the *Pediatric Rule* [14, 15].

The rule was designed to ensure that new drugs and biological products that are likely to be commonly used in children, or that represent a meaningful therapeutic benefit over existing treatments for children, contain adequate pediatric labeling for the approved indication at the time of, or soon after, approval. The rule would require a manufacturer of a new drug to submit, before approval, safety and effectiveness information in relevant pediatric age groups for the claimed indications. The submission of information could be deferred, e.g., if pediatric studies should not begin until information on adults had been collected, or in case the collection and filing of pediatric data would delay the availability of a product that provides a significant therapeutic advantage in adults.

Also in 1997, the Food and Drug Administration Modernization Act (FDAMA) introduced a process in which the FDA would develop a list of drugs for which additional pediatric information might be beneficial, agree on necessary studies, and issue to sponsors a Written Request (WR) for pediatric studies [16].

The WR includes a timeframe for completing such studies. In addition, the FDAMA provided an incentive for pharmaceutical companies to study products which would yield a health benefit in the pediatric population. If companies submitted studies responding to a WR, six additional months of marketing exclusivity were grante . Many drugs have received pediatric labeling under this provision, such that the FDAMA could be considered as the major legislative initiative that progressed pediatric drug development in the U.S. In 2001, the FDA's Report to Congress identified some drawbacks,. These drawbacks were partially addressed by the Best Pharmaceuticals for Children Act (BPCA) in 2002 [17].

The BPCA renewed the exclusivity incentives, created a process for on- and off-patent drugs involving government contracts for pediatric studies, and mandated public disclosure of study results . In 2003, the Pediatric Research Equity Act (PREA) was enacted, putting into legislation most components of the Pediatric Rule. It required pediatric assessment for certain applications unless waived or deferred and a pediatric plan that outlines the pediatric assessment (including timelines) and addressed development of an age-appropriate formulation.

In summary, there are two separate legislations for pediatric drug development in the U.S. the PREA defining the requirements and the BPCA defining the incentives. The PREA covers drugs and biologics and the studies are mandatory (only for indications under review, exempting orphan indications), whereas the BPCA covers only drugs and the studies are voluntary, relate to entire moiety, and might expand indications (including orphan indications). PREA and BPCA request pediatric studies to be labeled and pediatric safety data to be presented publicly to an advisory committee one year after study conduct. Both acts are clearly designed to encourage more pediatric research and more development of pediatric medicines.

In 2007, within the scope of the Food and Drug Administration Amendments Act (FDAAA), the PREA and the BPCA were amended and reauthorized.

E.U. perspective

In general, the objective of the E.U. regulation is to improve quality and ethical research into medicines for children, increase the availability of authorized medicines for children, and to increase available information on medicines for children without unnecessary studies in children and without delaying authorization for adults. Similar to the U.S., the European Medicines Agency (EMA) perceived the need for legal obligations for pharmaceutical companies to perform pediatric studies to obtain pediatric information for medicines used in children. In 1997, the European Commission organized a round table of experts to discuss pediatric medicines at the EMA. The experts identified the need to strengthen the legislation, in particular by introducing a system of incentives [12].

In December 2000, the European Health Council requested the Commission to take specific action to remedy the problem of usage of unauthorized medicinal products in the pediatric population [18].

One of the first steps of the Commission to address the problem was a consultation paper "Better medicines for children—proposed regulatory actions on paediatric medicinal products" (2002) [19].

In subsequent years, these proposals were assessed and resulted in a new legislation governing development and authorization of medicines for pediatric use. It was introduced in the European Union (E.U.) in December 2006 and entered into force January 2007 [20]

CHALLENGES IN THE DEVELOPMENT OF PEDIATRIC DOSAGE FORMS

The pediatric population spans a diverse range of physical size and developmental capabilities. This diversity drives the need for different formulations, a wide range of dosage strengths within each formulation, or titratable formulations. Clinical testing of prototype dosage

forms in the pediatric population is limited for ethical reasons and so these bioequivalence studies are performed in adults. Design requirements for oral formulations are primarily based on the patient age, body size and swallowing capability of the target population. Establishing the design requirements is generally complicated when the age range of the target population spans from birth to 8 or 10 years of age, as one specific type of dosage form is not ideal to cover this wide range. Information exists in the literature and from the European Medicines Agency (EMA) regarding possible acceptable dosage forms for various ages of patients [21].

For patients below 2 years, liquid dosage forms are widely acceptable. In some cases orally disintegrating or film strip-type formulations may also be acceptable; their safety profile with wide-spread use is, however, not known. Between the ages of 2 to 6 years, the ability of a child to swallow a small tablet or capsule is highly variable and many times based on the child's past experience with a particular drug or dosage form. A 2011 EMA guideline provides a guide on tablet size for various pediatric age groups; for example, tablets should be no larger than 5 mm for patients less than 6 years of age. Even so, this size can still be a challenge to swallow for many patients [22], so a liquid or orally disintegrating dosage form should be considered. When patients are over the age of 6 years, there is better acceptance of small to medium tablets intended for swallowing, but there is a significant percentage of the population that still has difficulty swallowing tablets or capsules. Most children 12 years and older can swallow a tablet or capsule of reasonable size, but what constitutes "reasonable" will vary from patient to patient. In addition to the dosage form itself, the number of strengths required is an important design issue. When the age or weight range of the treated population is wide, more flexibility in dosage strengths may be necessary. Liquid dosage forms are considered the most flexible in this regard, but liquid formulations carry some important limitations. Liquids must be accurately measured by the care-giver. If the liquid is a suspension, the bottle must be well shaken to suspend the drug and distribute it evenly throughout the liquid. Large multiple-use bottles are inconvenient to transport, and an accurate measuring device must be carried along with the bottle. Volume must be taken into consideration: too small, and the dose may be inaccurate; too large, and adherence will become problematic. Liquids also require preservatives, which may lead to excipient safety concerns. One significant liability associated with liquids is the potential for taste issues and the need for taste masking. Some flexibility in dosage administration can be achieved with granules or multi-particulate dosage forms, or by tablets that are intended to be orally disintegrating. These tablets can also be administered by dispersing the tablet in a liquid prior to administration but this requires that the care -giver estimate the correct portion of liquid to administer. Although direct administration with food or beverages should not be the primary design for a dosage form, the potential use of t hi s type of administration should be assessed and evaluated for stability and acceptability in patient [22].

When developing liquid dosage forms, the solubility and stability of the active pharmaceutical ingredient (API) is critical to designing an appropriate drug product. The API should be stable enough to allow for at least 18 months of shelf life for the intended commercial product. For APIs with high aqueous solubility and acceptable stability, it is generally easier to design a liquid dosage form as a solution that will have good dose uniformity. Special techniques are needed to develop liquid solutions with low aqueous solubility drugs. While an advantage of APIs with low aqueous solubility is that taste issues may be reduced, the challenge of dose uniformity when formulated as suspension increases significantly. Careful formulation development is required to ensure a suspension that can be accurately dosed with a reasonable amount of mixing .It is seldom practical or desirable to perform relative bioavailability studies in pediatric subjects. The initial prototype dosage form that is developed must be studied in adults in order to understand the *in vivo* performance. This is the general position of most regulatory agencies, although the US FDA does offer a potential exception for drugs that are classified as Biopharmaceutics Classification System (BCS) Class I [23].

This requirement needs to be factored into the overall development program for pediatric dosage forms. Recently, there has been discussion of whether the extrapolation of BCS data from adults to pediatric populations is appropriate [24].

The BCS system is based on a fundamental model of the gastrointestinal tract for the estimation of the extent of absorption, taking into account important physicochemical-physiological parameters such as aqueous solubility, intestinal permeability, drug dose, volume of luminal contents, fluid flow rate and intestinal surface area. Pediatric developmental changes must be taken into account, as they also play a key role in pharmacokinetics. For example, obvious maturation changes are related to the volume increase of luminal fluids, intestinal surface area and intestinal permeability [25-28]. Administered dose is also fundamentally important, and therefore there may be a need for a more quantitative, dose-dependent approach to pediatric BCS [29, 30]. Wu and Benet [31] have proposed an alternative Biopharmaceutics Drug Disposition.

Classification System (BDDCS) which includes the role of metabolism in classifying drugs. More research in this area, including potential development of a predictive dissolution testing method which could correlate *in vitro* data with *in vivo* product performance, would greatly simplify the development of pediatric dosage forms [32].

EXCIPIENTS IN THE PEDIATRIC FORMULATION: GENERAL CONSIDERATIONS

The choice of suitable excipients in a paediatric medicinal product is one of the key elements of its pharmaceutical development. Although the basic considerations regarding the use of a specific excipient are

similar for adult and paediatric preparations, the inclusion of any excipient in paediatric preparations, even those which are normally accepted for use in medicines for adults or those which are present in authorized paediatric medicines, requires special safety considerations. The intake of an excipient may result in a different exposure in children to that in adults, or in children of different ages. Also the excipient may have a different effect on developing organ systems. A conservative approach should be followed in case of limited safety data relevant to the use of an excipient in a specific age group.

Overall, the following aspects are to be considered when selecting an appropriate excipient for inclusion in a paediatric medicinal product:

• The function of the excipient in the formulation and potential alternatives;
• The safety profile of the excipient for children in the target age group(s) on the basis of single and daily exposure (and not the concentration or strength of the preparation);
• The expected duration of the treatment i.e. short term (single dose/few days) versus long term (weeks, months, chronic);
• The severity of the condition to be treated (e.g. life-threatening disease) and the therapeutic alternatives;
• The patient acceptability including palatability (e.g. local pain, taste); Allergies and sensitization.

In case the use of excipients with an identified risk cannot be avoided in the formulation of a particular pharmaceutical dosage form, the added value of the chosen pharmaceutical dosage form (and route of administration) should be well balanced against the possible use of other pharmaceutical dosage forms and routes of administration that do not require the use of such excipients. A comprehensive development rationale should be provided, taking into consideration the relative benefits and the risks of possible alternatives. While it is acknowledged that the use of a novel excipient (i.e. an excipient used for the first time in a medicinal product or by a new route of administration) is fundamental to pharmaceutical innovation and that the use of such novel excipients may be well justified by appropriate pre-clinical studies, it must be realized that safety issues may only become apparent when the product is used on a larger scale. Therefore, the added value of the novel excipient in a specific paediatric medicinal product must be well balanced against the use of other excipients with an established safety profile, other dosage forms or other routes of administration.

Allergies can arise in early childhood and children may be more easily sensitized than adults. In order to avoid sensitization and to expand treatment possibilities of allergic children, applicants should consider avoiding, where possible, excipients with a known potential to cause sensitization or allergies.

The relevance of the acquired data for the excipient in the proposed paediatric preparation should be summarised and discussed in relation to the target age group(s), indication, route of administration and type of dosage form, treatment duration, maximum daily intake of the excipient and exposure.

It is emphasized that it is the responsibility of the applicant to justify that each excipient in a paediatric preparation is safe for its intended use in the target age group(s). Toxicological studies may be necessary if the use of an existing excipient in a paediatric medicine cannot be justified on the basis of the aforementioned information sources [33].

AREAS FOR FUTURE RESEARCH

The need for improved oral pediatric dosage forms to optimize clinical care, with easy to swallow and palatable formulations in appropriate dosage increments, is overwhelming.

Areas for future research include

Validation of the BCS for children of all ages, or development of a modified, pediatric-specific BCS. Development of stream-lined, algorithm-based approaches to formulations development, potentially based on BCS classification of the API.

An Inter-Agency Agreement between NICHD and FDA is exploring this possibility Novel technologies for improving solubility and permeability with use of pediatric friendly and safe excipients. Scientific evaluation of pediatric excipients with long term history of use but which have reports of anecdotal adverse events in the literature. A rational approach for the determination of pediatric dose based on adult BE Studies Pediatric dosage form preferences for specific age and developmental stage. Research into economic models of small markets, including viable business models to reduce drug shortages and improve access to novel pediatric-friendly products [5].

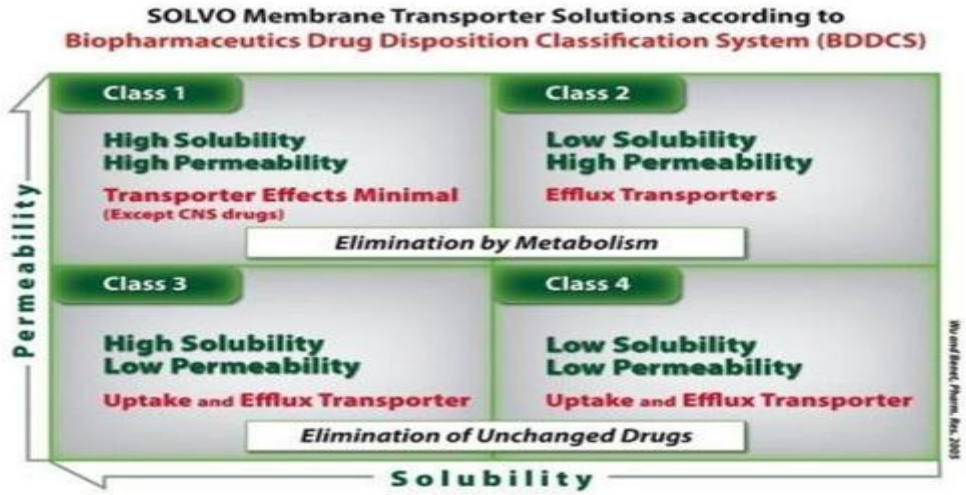
Table 1. Major milestones of pediatric legislation in the U.S

1994	1997	2002	2003	2007
Pediatric Labeling Rule	Pediatric Rule FDAMA: Food and Drug Administration Modernization Act	BPCA: Best Pharmaceutical For Children Act	PREA: Pediatric Research Equity Act	FDAAA: Food and Drug Administration Amendments Act

Table 2. Major milestones of pediatric legislation in the E.U

1997	1998	2000	2002	2006	2007
EMEA Round Tabel	ICH Discussion	Guideline ICH E11	Consultation Paper	Pediatric Regulation Agreed	Pediatric Regulation Into Force

Fig 1. Biopharmaceutics drug disposition classification system



CONCLUSION

Clinicians, patients and their care-givers, as well as society as a whole, place high value on pediatric clinical care. It necessarily follows that the availability of suitable pediatric dosage forms is of vital importance, as the availability of innovative, convenient and high-quality pediatric products can spells the difference between successful treatment of a pediatric patient or failure.

The pediatric population spans a diverse range of physical size and developmental capabilities. This diversity drives the need for different formulations, a wide range of dosage strengths within each formulation, or titratable formulations. Clinical testing of prototype dosage forms in the pediatric population is limited for ethical reasons and so these bioequivalence studies are performed in adults. Children's medications can be a challenge for physicians and pharmacists. Because most marketed drugs do not have U.S. Food and Drug Administration (FDA)-approved indications for pediatric use, physicians must prescribe them "off label." When drugs do not have labeled indications for children, drug manufacturers do not produce strengths and dosage forms appropriate for this patient population. Technological limitations are rarely the reason for the lack of pediatric formulations; rather, market conditions often dictate the types of drugs for which formulations suitable for children are made available.

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