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Review Article

Developing paediatric medicines: identifying the needs and recognizing the challenges

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Abstract

There is a significant need for research and development into paediatric medicines. Only a small fraction of the drugs marketed and utilized as therapeutic agents in children have been clinically evaluated. The majority of marketed drugs are either not labelled, or inadequately labelled, for use in paediatric patients. The absence of suitable medicines or critical safety and efficacy information poses significant risks to a particularly vulnerable patient population. However, there are many challenges associated with developing medicines for the paediatric population and this review paper is intended to highlight these. The paediatric population is made up of a wide range of individuals of substantially varied physical size, weight and stage of physiological development. Experimentation on children is considered by many to be unethical, resulting in difficulties in obtaining critical safety data. Clinical trials are subject to detailed scrutiny by the various regulatory bodies who have recently recognized the need for pharmaceutical companies to invest in paediatric medicines. The costs associated with paediatric product development could result in poor or negative return on investment and so incentives have been proposed by the EU and US regulatory bodies. Additionally, some commonly used excipients may be unsuitable for use in children; and some dosage forms may be undesirable to the paediatric population.

Introduction

One in five children (three million) within the United Kingdom has a long standing illness or disability (Martin 2004). Many, if not most, of these disadvantaged children will use medication on a long-term basis that is either unlicensed for paediatric use or has not been scientifically studied within this varied patient population, which includes a wide range of age groups (Table 1).

Around 90% of babies in neonatal intensive care, 70% of patients in paediatric intensive care, and almost 70% of children in hospital in Europe receive at least one unlicensed or off-label medicine during a hospital stay (Conroy 2003).

The situation is similar in the US, where only a small fraction of the drugs marketed and utilized as therapeutic agents in children have been clinically evaluated in paediatric patients (Woodcock 2001). Recent data indicated that the annual percentage increase in drug spending is rising faster in the paediatric population than in adults; and in parallel, that the numbers of children taking medicines is rising also (Steinbrook 2002).

The majority of marketed drugs are either not labelled, or inadequately labelled, for use in paediatric patients. Approximately 80% of listed patient information leaflets (PILs) in the US either disclaimed usage or lacked specific dosing information for paediatrics. Less than 30% of drugs approved by the US Food and Drug Administration (FDA) were authorized for paediatric use. Additionally, only 38% of new medicinal products, which were potentially of benefit in paediatric therapy, were initially labelled for paediatric use (Goldkind 2004).

A recent Australian survey of available PILs for paediatric patients (Tan et al 2003) showed either inadequate information (~70% of cases), or in those cases where there was specific paediatric information, absence of a suitable paediatric dosage form (~22% of cases). Considering that in many ways the diethylene glycol poisoning tragedy of the 1930s in the US was prompted by the unavailability of a child-friendly liquid preparation of the then new low solubility drug sulphanilamide, and as a result, chemists at the Massengill

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Table 1 Definition of paediatric sub-group by age and average weight

Paediatric sub-group	Age	Average weight (kg)
Pre-term newborn infants ('premature')	< 37-weeks gestation	<3.4
Full-term newborn infants ('neonates')	0–27 days	3.4
Infants and toddlers	28 days to 23 months	3.4–12.4
Children	2–11 years	12.4 to 39.0
Adolescents	12–16/18 years*	39.0–72.1 (male)/60.3 (female)

*Dependent on region as the legal age of consent varies from region to region e.g. in the US it is 17 years and in the UK it is 18 years.

pharmaceutical company formulated the drug in a non-aqueous solvent (diethylene glycol (Steinbrook 2002)), it appears that paediatric dosage form development has not moved on significantly in the succeeding 70 years.

This absence of critical safety and efficacy information poses significant risks to a particularly vulnerable patient population, particularly from over-dosing and resultant adverse events, or equally, under-dosing, and mistreatment of the underlying therapeutic disorder. Such under-dosing and over-dosing are the most common types of medication error in the paediatric population (Wong 2003).

Additionally, there are often inconsistencies in dosing information between 'therapeutically' equivalent generic products. Tan et al (2003) reviewed 133 generic medicines on the Australian market and 17 of those (13%) showed inconsistencies in their paediatric dosing information on their PILs. For furosemide 40 mg tablets, only 4/5 'therapeutically' equivalent generic products gave paediatric dosing instructions, and none were available in a 'child-friendly' product presentation. Inconsistent paediatric information was also observed for amitriptyline, clonazepam, clomifene, phenoxymethylpenicillin, amoxicillin, cephalexin and tamoxifen (Tan et al 2003).

This lack of vital, supporting information often prompts conservatism from paediatricians who often choose to prescribe existing, established medications. Though these products may have well established safety profiles, their efficacy may be marginal, and be potentially less effective than the newer drugs, which lack relevant safety data.

This is of particular concern, as children are not young adults and due to many physiological, regulatory, ethical and practical reasons, effective adult doses of newly approved medicinal products cannot be just prorated downwards based on a simplistic, relative mg/kg body weight basis. For these reasons, the first edition of the British National Formulary for Children (BNFC) was published in 2006.

The aim of this review is to illustrate the need for paediatric medicines and to identify the various challenges associated with the development of paediatric medicines. Various aspects including physiological and pharmacological, ethical, and regulatory are considered together with other challenges specific to the pharmaceutical industry and the formulation scientist.

Physiological and pharmacological challenges

Children are not just small adults, either from a biological or pharmacological development perspective. However, it is often overlooked that the paediatric patient population is not a homogenous sub-group either, and can be sub-classified, based on very real physiological (size and developmental biology) and pharmacology differences (RCPCH 1999) as shown in Table 1.

Pre-term newborn infants

It is not possible (except in rare cases) to extrapolate the efficacy of medicinal products from studies in adults. However, even studies in older paediatric patients can be difficult to extrapolate meaningfully to pre-term newborn infants (Guidance for Industry ICH E-11 2000). Clinical study design considerations that need to be evaluated include difficulties in assessing study outcomes; small patient numbers at each centre and very real centre differences (based on care, experience and infrastructure); small pharmacokinetic sampling (the total blood volume of a 0.5 kg pre-term infant is 40 mL) necessitating enhanced sampling and preparation techniques, and more sensitive analytical methodologies; and weight and age (gestational and postnatal).

More worryingly, this sub-group of the paediatric population is not homogenous, as there are huge developmental differences between a 25-week gestation newborn (0.5 kg) from the much heavier 30-week gestation newborn (1.5 kg). Important developmental biological and pharmacological features that need to be considered when administering medicines to pre-term paediatric patients include rapid changes of pharmacology and physiology necessitating unique dosing regimens; the immaturity of the renal and hepatic clearance mechanisms, and of the blood–brain barrier (this has the potential for all administered drugs to penetrate into the central nervous system (CNS), not just those that are reported to have high CNS permeability in adults); protein binding and displacement issues (in particular, bilirubin); opportunities (often inadvertent) for transdermal absorption of drugs; and unique neonatal susceptibilities e.g. retinopathy.

Full-term newborn infants

Although more mature, this is a similar sub-group to pre-term newborn infants. Drugs that demonstrate high protein binding in adults are often more freely available in neonates due to the competitive binding seen between albumin and bilirubin (elevated in neonates). The displacement of bilirubin can cause CNS toxicity as the blood–brain barrier is still not fully mature. This is a particular problem with sulphonamides.

The hepatic and renal clearance mechanisms are rapidly maturing in this paediatric sub-group. Consequently, hepatically cleared drugs are extracted more slowly, so drug doses and resultant efficacy need to be carefully monitored and potentially altered on a daily (or near daily) basis e.g. phenytoin, phenobarbital. The body water, fat content and high surface area to weight ratio of newborn paediatric patients indicate that the volumes of distribution of drugs may be significantly different to older paediatric or adult patients. As a consequence water soluble drugs are diluted to a greater extent in neonates resulting in the potential requirement to

increase dose to produce the desired plasma concentration (Duke & Urquhart 1997).

One of the most important differences between paediatric and adult patients is oxygen consumption, which in infants may exceed 6 mL kg^{-1} min^{-1}, twice that of adults (Rusy & Usaleva 1998). There are physiological adaptations in paediatric cardiac and respiratory systems to meet this increased demand. Both induction and emergence from anaesthesia are more rapid in children than in adults. This is probably because of a smaller lung functional residual capacity per unit body weight and a greater tissue blood flow, especially to the key organs (brain, heart, liver and kidney). These organs in adults account for 10% body weight vs 22% in neonates. These differences can result in differences in drug clearance and ultimately pharmacokinetic parameters for drugs administered to this sub-group compared with older infants and children.

Similarly, oral absorption is less predictable than in older paediatric or adult patients. In the early days after birth, neonates are achlorohydric, with gastric pH being much higher than in the majority of Caucasian adults. As a consequence, the absorption of acid labile drugs may be enhanced e.g. proton pump inhibitors, whereas the absorption of fat soluble drugs may be reduced, for example fat soluble vitamins (Duke & Urquhart 1997). This difference in gastric pH reported for neonates would pose additional challenges for the development of pH-dependent drug delivery systems for administration to neonates. There are many literature examples of unanticipated toxic effects from limited clearance and resultant accumulation of drugs in this class of infants; for example, chloramphenicol grey baby syndrome (Mulhall et al 1983). In contrast, established toxicology profiles may be less applicable to this patient sub-group; for example, aminoglycosides are safe and effective in neonates (Nestaas et al 2005), whereas nephrotoxicity is commonly encountered from these drugs in an older patient sub-group.

Infants and toddlers (28 days to 23 months)

This is a period of very rapid growth and maturation. Oral absorption becomes much more reliable, adult gastric pH is achieved by 23 months, and clearance mechanisms are maturing rapidly (but with significant intra-subject variability due to differences in physical growth and organ maturation rate between individuals), and with clearance (based on a mg/kg basis) often exceeding that seen in adults. This is as a result of the liver being up to 50% greater (as a percentage of total body weight) than in adults. As a consequence the administered doses for hepatically cleared drugs may need to be higher than in adults. The rates of gastric emptying and general gut motility fall during infancy and early childhood. Although, the extent of drug absorption is usually not impacted, the rate may be, i.e. the maximum blood plasma concentration (C_{max}) increases, but the area under the blood plasma concentration vs time curve (AUC) remains the same; consequently sustained release formulations should be used with caution during childhood (Duke & Urquhart 1997).

Children (2–11 years)

Most drug clearance pathways have matured in this subgroup; however, clearance values again often exceed adult values, and are often dependent on the maturation of specific metabolic pathways. Neonates and children have greater surface area to weight ratios and a thinner stratum corneum than adults. Consequently, there is greater potential for high systemic exposure and subsequent adverse events from topical application of drugs. Of particular importance to the study of drugs in this sub-group is the impact on growth and development. CNS-active drugs can adversely affect psychomotor skills in pre-school/school age groups and impact on the efficacy end-points. The impact of the drug on the child can be monitored using developmental end points, such as growth, weight gain and school performance.

Rectally administered drugs can produce variable and erratic systemic absorption, but can still be a valuable route of administration, especially in the very young, who can experience difficulties swallowing solid oral dosage forms, and which, thereby avoid the need for injections or in emergency use, such as prolonged fitting e.g. rectal diazepam (EMEA 2003, 2005). As the absorption of subcutaneous or intramuscular injectables are largely dependent on tissue perfusion, minor variations in absorption are relatively unimportant.

Puberty can impact on the efficacy of metabolizing enzymes, which significantly impacts on the administered dose on a mg/kg basis, of certain drugs, for example theophylline (Conroy 2003) due to the influence of such enzymes on drug elimination and consequently the half-life. It may be appropriate to study the impact of puberty on certain medicinal products, or monitor the biological markers of puberty and indirectly assess the impact of the drug. Puberty is highly variable and is different in the sexes, girls maturing earlier (as young as nine years) and more rapidly.

Children often benefit from drugs with intrinsically long half-lives or modified release dosage forms as they can be administered once-daily. The compliance and ethical issues of teachers and carers administering medicinal products should not be underestimated, e.g. Ritalin (Drug and Alcohol Education and Prevention Team 2005).

Adolescents

The impact of any medicinal product on the physical, mental or sexual maturation of this paediatric sub-group needs to be evaluated. As with late-phase infants, the impact on puberty is important. In particular, the impact on hormones (especially sex hormones), sexual activity and the need for contraception or pregnancy testing can be important factors in clinical trial design. Several disease states are influenced by hormonal changes, for example, changes of frequency and severity of asthma and migraine. However, non-compliance is particularly acute in this age range and recreational drug use, for example, alcohol, tobacco, cocaine, ecstasy, etc., is unfortunately becoming more prevalent.

Such biopharmaceutical differences between adults and paediatrics, as summarized in Table 2, can affect the administration, distribution, metabolism and elimination (ADME) of drugs and hence, the required dose. For example, midazolam shows a higher risk of serious adverse events in paediatrics with pulmonary hypertension and congenital heart disease, as lower doses than predicted, based on a purely mg/kg basis, are required. In contrast, gabapentin requires higher doses in paediatrics less than five years of age, to control seizures.

Table 2 A summary of the major biopharmaceutical differences between paediatrics and adults

Biopharmaceutical parameters	Paediatric compared with adult
Gastric pH	Neonates achlorohydric; pH much higher than in adults
Clearance rate	Greater in infants and children than adults
Gastric emptying	Faster in neonates than adults; slower in infants and children than adults

In addition, new adverse events have been reported in children under 12 years of age (hostility and aggression). Similarly, etodolac which is used to treat childhood arthritis requires doses of 2- or 3-times the adult dose, on a mg/kg basis (Woodcock 2001).

Ethical challenges

There is a growing body of opinion within the world-wide community that children (and their parents) have the right to properly researched and regulated medicines (Davies 2004). Unfortunately, there is an equally strong lobby that considers experimentation on children (particularly placebo-controlled study designs) to be unethical, and for this to be ultimately a potentially profitable exercise, to be morally indefensible. Consequently, the availability of financial incentives, in terms of patent life extensions and exclusivity, for industry to develop paediatric medicines in the US and EU is viewed by some as setting an unwanted precedent.

Before undertaking any paediatric research, the investigator needs to ensure that such research cannot be done in adults and the results extrapolated to children. The overarching purpose is to obtain knowledge, applicable to the wider needs of the paediatric community.

The paediatric sub-group represents a particularly vulnerable patient group. As such, special measures and precautions are required to protect the participants (or their parents, if they are of an age where informed consent is not practicable) from undue risks. Some of the issues perceived by parents (Martin 2004) include: risks (both known and unknown); discomfort to the child, especially from invasive treatments; disruption to routine and to family schedules; financial impact; incentive to change (if current regimen is working well); poor communication, both in terms of ongoing issues and feedback on trial results; and scepticism on the real goals of the researchers (more focussed on the research, rather than the treatment and care of the child). However, rights and duties are 'two sides of the same coin'. If there is a strong lobby for accessibility to paediatric medicines via well designed and controlled clinical studies, is there an associated duty for families to become involved in such trials? Unfortunately, even world-renowned ethics advisors are at a loss to answer this key question (Davies 2004).

However, participation in any clinical trial involves the issue of risk/benefit, which needs to be carefully evaluated by the overseeing Independent Ethics Committee and Institutional Review Boards. Additionally, The UK Medicines for Children Research Network (2007) has been created to facilitate the conduct of randomized prospective trials and other well-designed studies of medicines for children. Together, such organizations should ensure that participation in such studies is free from inappropriate inducements, and any reimbursement and subsistence costs are appropriate. In clinical trials involving infants and children, participants are unable to provide informed consent (or assent). This must be obtained from parents or guardians and results in both the paediatric patient and his/her parent or guardian being 'screened' and recruited to the study. The issue of consent is even further complicated where adolescents are to be considered, as here the competent adolescent patient is able to provide informed consent. In all cases parallel consent from the parents is ideal and participants should be made aware of their rights to withdraw from the trial at any time, except in those very rare instances where the welfare of the participant would be placed in jeopardy by failing to participate, or continuing to participate in the clinical programme.

A meta-analysis of all clinical asthma studies over a three-year period was recently published (Coffey et al 2004). It covered 70 studies and reviewed paediatric sub-groups in 74% of these cases. Of the 70 studies, 63% were double-blind placebo-controlled, but 13% of these studies reported discontinuation of the appropriate therapy. Of those studies investigating children and adults, 15% clearly differentiated between the two patient sub-groups at baseline, whereas 2% showed differences in the results analysis. However, 85% of these studies assessing both patient sub-groups failed to characterize age in the discussions.

The meta-analysis revealed that children in the placebo arm of asthma studies were twice as likely to withdraw because of disease exacerbations, compared with those receiving active medication. Sub-group analysis could not be performed in the majority of cases, and perhaps, most worryingly, children were being exposed to increased risk, without clear advancement in paediatric science. Based on this investigation there is a clear need to define the various risk categories and the related consent process, to better assess the benefits to be accrued by pursuance of these paediatric studies, and to better assess the therapeutic disorder or condition, as it relates to the paediatric sub-group. The ethics of conducting placebo-controlled paediatric studies is still a matter of great concern and hampers meaningful investigations in many therapeutic areas.

Minimizing the risk to the participants should be the principal objective, even if the whole community benefits; and every effort should be made to anticipate or reduce known risks. There should be full awareness of the known pharmacology, toxicology, safety and efficacy of the medicinal product before initiation of the study. In addition, the studies should be conducted by trained paediatricians, with knowledge and experience of dealing with paediatric adverse events. The number of participants should be as low as is commensurate with appropriate study designs, whilst being sufficiently powered to ensure statistical significance for results obtained. Processes for ensuring rapid termination of a study should be in place, should additional, unanticipated risks emerge. In particular the approaches to reduce invasive procedures and minimize number and volume of samples for subsequent pharmacokinetic evaluation should form part of

the study protocol. Such constraints are likely to result in innovative study designs being proposed to maximize the amount of pharmacokinetic, pharmacodynamic and safety data that may be obtained from the study (Feldman et al 2001; Lovell et al 2003).

The US FDA, under the auspices of the Pediatric Advisory Subcommittee (PAS), has taken steps to reassure the general public that the safety of participating children is of paramount concern (Woodcock 2001). The PAS has addressed several of these ethical issues, including: children as volunteers vs paediatric patient studies; placebo-controlled trials; and clinical trial design and data analysis. To specifically provide additional safeguards for children, to ensure compliance with the Children's Health Act of 2000, and to coordinate these regulations with Health and Human Services regulations the FDA introduced Additional Safeguards for Children in Clinical Investigations of FDA Regulated Products (FDA 2001).

The factors affecting the need for paediatric investigation of either an established drug, or a newly developed drug, and the nature of this clinical programme are varied. They include: the seriousness of the condition requiring treatment; the prevalence of that condition in the paediatric sub-group; whether the medicine is 'first in its class', or another representative of an established class of compounds; the availability and suitability of alternative treatments, especially the safety and efficacy of these alternative treatments; the need to develop paediatric specific end-points in the therapeutic disorder; unique safety concerns; research that indicates that there could be unique paediatric applications for this medicinal product; the likely age ranges of the paediatric population; and the need for paediatric formulation development.

Regulatory challenges

During 1997, as part of the FDA Modernization Act the US Congress provided new marketing incentives to companies who conducted paediatric studies (Table 3). The paediatric exclusivity provision provides for a six-month additional exclusivity or additional patent protection in return for performing clinical studies in children. The Pediatric Final Rule (1998) enabled the FDA to require manufacturers of new and established drugs to conduct paediatric studies if the product were likely to provide meaningful therapeutic benefit or would be used in a significant number of paediatric patients, compared with existing treatments. The FDA subsequently published a list of drugs where paediatric data would be beneficial, worked with industry to develop written requests for paediatric studies, reviewed submitted protocols, and made exclusivity determinations. This was facilitated by industry guidance covering: Qualifying for Pediatric Exclusivity (Guidance for Industry September 1999); Pediatric Oncology Studies in Response to a Written Request (Guidance for Industry draft June 2000); and General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (Guidance for Industry draft November 1998). Additionally, the FDA contributed to an international guidance; ICH-E11, Clinical Investigations of Medicinal Products in Pediatric Populations (December 2000).

By 2004, the FDA had reviewed (Goldkind 2004) over 660 studies covering paediatric efficacy/safety (35%), pharmacokinetics/safety (29%), pharmacokinetics/pharmacodynamics (9%), safety (16%), and other studies (9%). Where efficacy studies were designed to demonstrate that the drug worked for its intended use, safety studies were designed to determine risk and appropriate safety at certain drug levels, pharmacokinetic studies measured drug levels in paediatric patients, as well as the rate of absorption, distribution and elimination; and pharmacodynamic studies to evaluate the impact of the drug and how the child reacted to the drug. This covered over 31 000 paediatric patients and resulted in over 70 label changes.

The Children's Health Act mandated that research on children conformed to the Protection of Human subjects regulations (45 CFR 46). Similarly, the Best Pharmaceuticals for Children Act (BPCA, January 2002) re-authorized paediatric exclusivity, established a process for the study of paediatric applications of generic drugs, mandated that the FDA and National Institutes of Health collaborate to study paediatric applications of non-generic drugs that industry had elected not to investigate, and mandated publication of new findings in paediatric medicine. The BPCA further mandated that the paediatric study protocols would ensure adequate representation of ethnic and racial minorities, added neonates (where appropriate), and mandated the formation of the Office of Pediatric Therapeutics.

The Pediatric Research Equity Act (PREA) 2003 requires that paediatric studies be performed in all relevant sub-groups for applicable drugs and biological products and established a Pediatric Advisory Committee (PAC). Finally, paediatric measures for counter terrorism have been drafted under the auspices of the Division of Pediatric Drug Development, which cover topics such as paediatric vaccines, chemical agents, radiation emergencies and anthrax infections.

In parallel, the European Commission introduced a proposal for the regulation and control of medicines for paediatric use. The proposal covered the following areas: to increase

Table 3 A comparison of the EU and the US paediatric legislation

	EU	US PREA	US BPCA
Regulatory body	EMEA	FDA	FDA
Mandatory	Yes	Yes	No
Incentive	Six-month extension to Supplementary Protection Certificate	Paediatric indication approved and labelling amended	Six-month patent extension
Off-patent drugs	PUMA—10 year exclusivity	Not applicable	National Institutes of Health and FDA can provide funds if unmet paediatric clinical need.

development of paediatric medicines; to avoid subjecting children to unnecessary clinical investigations; to ensure and encourage the research into paediatric medicines; to ensure and encourage the development of paediatric dosage forms; and to improve labelling of paediatric medicines (Dunne 2004).

The proposal established a new subcommittee of the European Medicines Evaluation Agency (EMEA): the European Paediatric Committee (EPC). This committee would comprise membership from the CHMP (Committee for Medicinal Products for Human Use), representatives from the member states and independent stakeholders nominated by the European Commission (patient organization, paediatricians, etc.).

The EPC would address the five main objectives of the proposal and develop and legalize the ingredients of the Paediatric Investigation Plan (PIP), which will be a requirement for all new paediatric products. The PIP will cover all appropriate paediatric patient sub-groups that would be covered by the new product. The PIP does not cover recognized generics, herbal, homeopathic or medicinal products claiming 'established uses'. However, it does include existing products, still enjoying patent coverage, where these cover new paediatric indications, new 'paediatric-friendly' routes of administration and new paediatric dosage forms. Although companies submitting new Marketing Authorization Applications (MAA) can investigate deferral of inclusion of results from the PIP at the time of the application the MAA would still need to include the agreed PIP, together with a timetable for completion and submission of the results from the PIP. A PIP waiver could be granted if the EPC considered that the new product was inappropriate for paediatric use, or could be unsafe or ineffective in paediatric use, or that the existing therapeutic area was sufficiently well covered by existing paediatric products. The EPC will consider all aspects of the PIP and any anticipated therapeutic benefits.

For established generic medicinal products, there would be incentives provided for the development of paediatric indications (or products) in concurrence with an agreed PIP. There would be eight-years' data protection and 10-years' marketing protection covering these paediatric studies, and any formulation specific data. This is a similar situation to existing regulations for new medicinal products. The proposal establishes a Paediatric Use Marketing Authorisation (PUMA), which would be eligible for a centralized procedure. In addition, member states can offer additional incentives to encourage paediatric research and development.

For new medicinal products, there will be a six-month extension to the existing Supplementary Protection Certificate if the PIP criteria are fulfilled. The relevant information must be incorporated into the Summary of Product Characteristics (SmPC) and there must be an approved MAA in all member states. In addition, similar incentives would be applied to Orphan Products, including an extra two-year market exclusivity, from the existing ten to twelve years.

The proposal would also establish a paediatric clinical trials network, coordinated by the EMEA, and separate from the national procedures and a European-wide clinical trials database. The EPC would give free scientific advice to interested parties. The EPC would identify the most pressing paediatric needs on a therapeutic basis to help prioritize investigations and to assist in decision making (Dunne 2004).

Development challenges to the pharmaceutical industry

Pharmaceutical companies developing medicinal products in new therapeutic indications are often viewed from the outside as considering clinical studies in children to be an unattractive, non-viable or non-profitable option (Conroy et al 2000). However, industry has long recognized the need for paediatric medicines and for nearly a decade has been calling for medicines to be licensed to children of specific age ranges, for the publishing of paediatric clinical research guidelines and for regulatory guidance in this area (BPA/ABPI 1996).

Unfortunately, there are issues for the pharmaceutical industry in this area. Despite the numbers of children affected in the developed world the paediatric market is still comparatively small. It has been estimated that the cost of a paediatric development plan for a new medicinal product is in the order of $20 million, and for an existing product that could equate to a poor, or even negative, return on investment (Tiner 2004). The objectives of the proposed regulations in the EU and US are to improve the overall health and welfare of children, by increasing research, development and approval of paediatric medicinal products. However, it is not clear that the existing incentives will lead to more paediatric research in the EU, as the EU patent extension period is no improvement on the current US position. Although there are some incentives to encourage the generic industry to carry out more research, or develop new paediatric dosage forms on older established products, the generic industry has no record of innovative research to fall back on, which may hamper future development. This is obviously unfortunate as there are often large knowledge gaps with the existing products as many of them have been used 'off-label' and there is no incentive to publish this information, particularly when there is often no obvious advancement in the particular field of research.

In the US the paediatric exclusivity provision has been highly effective, with industry responding positively, and with resultant extensive paediatric health benefits. In the three-year period covering implementation of the guidance to 2001, there were 218 paediatric proposals from industry, 188 Written Requests from FDA, 77 incomplete letters issued in place of a Written Request, and 95 amendments to Written Requests after negotiations between FDA and industry. This resulted in the submission of 34 products (which included paediatric studies as part of the NDA (New Drug Application) submission), and of 28 products (82%) being granted paediatric exclusivity. The complete list can be found on the FDA website (www.fda.gov/cder/pediatric/wrlist.htm), and includes drugs for the treatment of HIV, diabetes, hypertension, obsessive compulsive disorders, allergies, juvenile rheumatoid arthritis and seizures. It has been estimated that industry had completed 80% of the paediatric studies requested by FDA, which is in contrast to the 15% completion rate in the six-year period before the initiation of the paediatric exclusivity provision (Woodcock 2001).

Formulation challenges

Toxicity issues of some common excipients in paediatric formulations

As previously described, one of the greatest medicinal tragedies of the last century (diethylene glycol poisoning) was prompted in many ways by the need to develop 'child-friendly' dosage forms (Geiling & Cannon 1938). At that time clinical safety of new medicines and new formulations was not required; nor was there an extensive safety data base on existing or novel excipients. In the resulting tragedy, 107 patients died of diethylene glycol poisoning, many of them children (Steinbrook 2002).

Today, we have a well established safety data base on existing excipients, and new excipients are required to undergo extensive animal safety testing before they can be used in clinical studies. However, the toxicity of some common excipients (Table 4), like lactose, may differ across the various paediatric sub-groups and between paediatrics and adult patient groups (Edge et al 2005). Maximum tolerated doses for excipients, determined by animal safety testing, are usually referenced for use in adults and are not necessarily directly applicable to their use in children.

One of the direct consequences of the need for oral liquid preparations (that children typically find easiest to swallow), is that taste-masking which often relies on sweeteners is

Table 4 Examples of potential risks associated with frequently used pharmaceutical excipients

Excipient	Example of function	Example of potential risk	Reference
Almond oil	Emollient	Dermatitis	Guillet & Guillet 2000 Golightly et al 1988
Aspartame	Sweetener	Hyperactivity	Butchko & Kotsonis 1989 Wolraich et al 1994 Gershanik et al 1981
Benzyl alcohol	Antimicrobial preservative	Fatalities	Brown et al 1982 Gershanik et al 1982 McCloskey et al 1986
Carrageenan	Suspending agent	Induces inflammatory responses in animals	MAFF 1992
Diethylene glycol	Vehicle	Poisoning	Steinbrook 2002
Docusate sodium	Wetting agent	Diarrhoea	Guidott 1996
Lactic acid	Skin softener and preservative	Neonates have difficulty metabolizing the *R* isomer	WHO 1974
Lactose	Diluent in tablets, carrier in powder inhalers etc.	Lactose intolerance	Suarez & Saviano 1997 Edge et al 2005
Mineral oil	Emollient, lubricant	Lipoid pneumonia	Becton et al 1984 Prakesh & Rosenow 1990 Owen 2005
Peanut oil	Solvent	Hypersensitivity	Monerat-Vautrin et al 1991 Brown 1991 De Montis et al 1993 Lever 1996 Wistow & Bassan 1999
Polysorbates	Solubilizing agents, wetting agents etc.	Death (when administered with Vitamin E intravenous preparations)	Alade et al 1986 Balistreri et al 1986
Propyl gallate	Antioxidant	Methaemoglobinaemia	Nitzan et al 1979
Propylene glycol	Solvent and antimicrobial preservative	CNS adverse events	Martin & Finberg 1970 Arulanantham & Genel 1978 MacDonald et al 1987
Sodium benzoate	Antimicrobial preservative	Non-immunological contact reactions	Nair 2001 Edwards & Voegeli 1984
Talc	Glidant, lubricant	Severe respiratory distress	Pairaudeau et al 1991
Tartrazine (FD&C Yellow No.5)	Colorant	Hyperactivity	Pollock et al 1989 Ward 1990 Bell 1991 Levesque 1991 Dietemann-Molard et al 1991 Mroz 2003
Thimerosal	Antimicrobial preservative	Toxic	Ford et al 1985 Cox & Forsyth 1988 Seal et al 1991 Noel et al 1991

essential. Aspartame is used as an intense sweetener in beverages, food products, and in pharmaceutical preparations. It enhances flavour systems and can be used to taste-mask unpleasantly bitter tasting characteristics of common drugs. A number of adverse events have been reported following the consumption of large quantities of aspartame in beverages (Golightly et al 1988; Butchko & Kotsonis 1989). Although aspartame has been blamed for hyperactivity in children; a double-blind study of 48 pre-school children who were dosed with diets containing $38 \pm 13\,mg\,kg^{-1}$ body weight of aspartame for three weeks showed no appreciable adverse behaviour or impact on cognitive function (Wolraich et al 1994).

The development of multi-dose oral liquid and parenteral preparations also necessitates the requirement for preservatives to prevent microbial contamination, as serious microbial infections in the very young can often be fatal.

Benzyl alcohol is an antimicrobial preservative used in cosmetics, food, and in a wide range of pharmaceutical preparations including oral liquid and parenteral preparations. Although widely utilized, its use has been associated with some fatal adverse reactions when given to neonates (Gershanik et al 1981). It is now recommended that its use as a parenteral preservative for new born infants is discontinued. The fatal toxic syndrome in low birth weight premature children was attributed to the use of benzyl alcohol preservative in solutions used to flush-out umbilical catheters (Brown et al 1982; Gershanik et al 1982; McCloskey et al 1986). The FDA subsequently recommended discontinuation of this practice, and of the use of medicinal products containing preservatives in neonates (Belson 1982; FDA 1982).

Sodium benzoate is an antimicrobial preservative used in cosmetics, food, and in a wide range of pharmaceutical preparations. It has been shown to elicit non-immunological contact reactions, including urticaria and this should be taken into account when formulating paediatric products (Nair 2001). In addition, it is recommended that parenteral combinations of caffeine and sodium benzoate should not be used in neonates (Edwards & Voegeli 1984).

Thimerosal is an antimicrobial preservative used in cosmetics, soft contact lens solutions, and in some pharmaceutical preparations. However, its use is declining owing to its toxicity and there are suggestions for discontinuing its use in eye drops (Ford et al 1985) and vaccines (Cox & Forsyth 1988; Noel et al 1991; Seal et al 1991). In the US and EU, regulatory bodies have recommended that its use in vaccines, particularly paediatric vaccines, is discontinued (AAP 1999; EMEA 1999). In recent years public pressure groups have tried to link thimerosal in paediatric vaccines with autism but this claim was unsubstantiated and repudiated by regulatory agencies (DoH 2001).

Propyl gallate is a widely used antioxidant in cosmetics, food, and in a wide range of pharmaceutical preparations. Although, propyl gallate has strong sensitizing potential in animals there are few reports of adverse events in man, but do include methaemoglobinaemia in neonates (Nitzan et al 1979).

Oral liquid formulations are often complimentarily coloured and flavoured to aid in paediatric patient acceptance and long-term compliance. For instance, a paediatric formulation might be taste-masked using banana flavour (a particular favourite of many young children), which would be complimented by the addition of a yellow colorant. One such colorant (FD&C Yellow No. 5 or tartrazine) has long been the subject of much controversy centred around its safety profile, and its possible link with hives (reported incidences of 0.001%) and hyperactivity in children (Ward 1990). In the US, any prescription drug containing tartrazine is labelled: "This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic reactions (including bronchial asthma) in certain susceptible persons." (Mroz 2003).

Generally, concerns over the safety profile of colorants in pharmaceuticals and foods are associated with hypersensitivity and hyperactivity (Bell 1991; Dietemann-Molard et al 1991; Lévesque et al 1991), especially in children (Pollock et al 1989).

Poorly soluble drugs are often prepared as oral suspensions, and are frequently co-formulated with surfactants to aid in the wetting of the drug, and in its subsequent dissolution. Docusate sodium, an anionic surfactant, is widely used in pharmaceutical preparations as a wetting agent, dissolution aid, and as laxative and faecal softeners. However, the levels of docusate sodium should be strictly controlled in medicinal products to prevent unwanted incidences of diarrhoea, especially in infants. The adult dose (500 mg) is over six-times the amount administered to children of six months (75 mg) and older (Guidott 1996).

Polyoxyethylene sorbitan fatty acid esters (Polysorbates 20, 40 and 60) are used as emulsifying agents, non-ionic surfactants, solubilizing agents, wetting, dispersing and suspending agents. Polysorbates are generally regarded as non-toxic and non-irritant materials; however, they have been associated with serious adverse events, including some deaths, in neonates who were administrated with vitamin E intravenous preparations (Alade et al 1986; Balistreri et al 1986).

Carrageenan is a naturally occurring gel base or suspending agent derived from seaweed extracts. Carrageenan is generally considered to be non-toxic and non-irritating, except in parenteral preparations. However, because of its ability to induce inflammatory responses in animals, the UK Food Advisory Committee did recommend the removal of carrageenan as an additive in infant food formulas (MAFF 1992).

Lactic acid is used in beverages, food, cosmetics and pharmaceuticals. In topical cosmetics it is used as a skin softener. In food and beverages it is used as a preservative. It is usually present as the racemate (*RS*), but in some cases the *S* isomer predominates. Lactic acid is the naturally occurring endpoint of anaerobic metabolism of carbohydrates so is usually viewed as being non-toxic at the levels used in typical formulations. However, there is evidence that neonates have difficulty metabolizing the *R* isomer, and hence this isomer and the racemate should not be used in infant formulas for children less than three-months old (WHO 1974).

Almond oil is used as an emollient in infant skin-care preparations. Although typically regarded as non-toxic and non-irritant, there has been one case reported in the literature of a five-month-old child developing contact dermatitis, which was attributed to the topical application for a two-month period to the cheeks and buttocks (Guillet & Guillet 2000).

Mineral oil is used as an emollient, lubricant or oleaginous vehicle. The most serious adverse event caused by this excipient is lipoid pneumonia caused by inhalation of the oil, as it does not elicit the cough reflex. With the reduction in the use of this excipient in intra-nasal formulations the incidence of lipoid pneumonia has decreased (Owen 2005). However, this condition has been associated with the use of mineral oil in cosmetics in an adolescent (Becton et al 1984) and in ophthalmic formulations (Prakesh & Rosenow 1990). It is recommended that this excipient is not used in paediatric formulations.

Peanut oil is used as a food additive and as a solvent in intramuscular injections. Some workers have suggested that the use of peanut oil in childhood (infant formula and topical preparations) can lead to later episodes of hypersensitivity, and therefore should be discontinued (Brown 1991; Monerat-Vautrin et al 1991; De Montis et al 1993; Lever 1996; Wistow & Bassan 1999). Consideration must also be given to the potential risk of nut allergies.

Propylene glycol is a general solvent and antimicrobial preservative used in a wide range of pharmaceutical preparations including oral liquid, topical and parenteral preparations. Its use in large volumes in children is discouraged, and it has been associated with CNS adverse events, especially in neonates (Martin & Finberg 1970; Arulanantham & Genel 1978; MacDonald et al 1987).

Lactose occurs widely in dairy products and is used in infant feed formulas. In pharmaceutical preparations it is widely used as a diluent in tablets and capsules, in lyophilized powders, and as a carrier in dry-powder inhalation products. Lactose intolerance occurs when there is a deficiency in the intestinal enzyme lactase. This enzyme is normally present at high levels at birth, declining rapidly in early childhood. Hypolactasia (malabsorption of lactose) can thus occur at an early age (4–8 years) and varies among different ethnic groups (Suarez & Saviano 1997). It is unlikely that severe gastrointestinal adverse events could result from ingestion of medicinal products in adults, but it is less clear if this is equally applicable in infants.

Talc is commonly used as a dusting powder and historically has been used as a glidant and lubricant. Although generally regarded as non-toxic when orally ingested, inhalation of talc causes irritation and severe respiratory distress in children (Pairaudeau et al 1991).

Palatability challenges

Taste is the most important parameter governing paediatric patient compliance. Consequently, those administering foul tasting drugs to children often resort to combining medication with food or fruit juice. Though this may 'mask' the taste of the tablet, this could have a detrimental influence on efficacy and safety for a variety of reasons e.g. affecting bioavailability, and inaccurate dosing.

Unfortunately, undesirable palatability is one of the most important formulation challenges encountered with the majority of drug substances. To overcome this issue several approaches have been utilized including the use of flavours, sweeteners, amino acids, polymer coating, conventional granulation, lipids, including lipid emulsions and liposomes, lecithins, complexes with cyclodextrins and ion-exchange resins, salts, and polymeric materials.

The use of flavours, generally in combination with artificial sweeteners, is by far the most commonly utilized approach in paediatric formulations, but is not the most successful for highly soluble or very bitter drugs. Artificial flavours (grape, cherry, raspberry etc.) have been used to mask the taste of some saline drugs (Lankford & Becker 1951). The combination of an effervescent citrate couple in combination with cream and orange flavours was used to mask the bitter taste of chlorphenamine and phenylpropylamine (Brideau 1995), lemon flavour was used to mask the taste of famotidine (Wehling & Schuehle 1993a), whilst cherry flavour was used to mask the flavour of paracetamol (Wehling & Schuehle 1993b). Vitamin B oral solutions, inosinate and fruit flavours (particularly orange) are reported to have improved taste (Kobayashi et al 1992).

Monosodium glyceryrrhizinate, an artificial sweetener with a longer-acting sweetness, and flavours have been utilized to improve the bitter taste of guaifenesin (Fawzy et al 1998). Low levels of ammonium glyceryrrhizinate are used to mask the bitter tastes of chewable multivitamin and analgesic tablet formulations, cough and cold syrups, and oral antibiotics (Kurtz & Fuller 1993). Sorbitol, sodium saccharin, sodium glutamate and vanilla flavours have been used to produce palatable solutions of theophylline (Maegaki et al 1993).

Lipids can be used to coat the buccal cavity (including the taste buds) and reduce the flavour threshold of bitter tasting molecules. Cimetidine can be taste masked by granulation with the lipid lubricant, glyceryl monostearate (Gottwald et al 1991). Similarly, gabapentin can be mixed with gelatine, partially hydrogenated soybean oil and glyceryl monostearate (Chau & Cherukuri 1991). Palatable syrups of carbetapentanecitratem diphenylhydramine, paracetamol and noscapine can be prepared using glycerine, polygylcerine fatty acid esters and triglycerides (Miura et al 1992).

Formulations using lecithin, or related compounds can improve the taste of bitter drugs. Soybean lecithin has been used to mask the unpleasant taste of the antibiotic, talampicillin (Kinoshita & Shibuya 1987). Similarly, suspensions of phosphatidic acid and β-lactoglobulin suppress the bitter tastes of caffeine, quinine and papaverine (Kasturagi & Kurihara 1993).

Coating of bitter tasting drugs with hydrophilic agents provides one of the most straightforward approaches to taste masking. The unpleasant taste of ibuprofen in a suspension formulation can be taste masked (Motola et al 1995), using a mixture of carmellose sodium and sweeteners (sucrose, sorbitol and glycerine). The bitter tasting antibiotic, amoxicillin, can be taste masked by granulating with microcrystalline cellulose and then mixing with hydroxypropylcellulose (Olthoff et al 1988). Triprolidine can be taste masked using hydroxypropylcellulose, sweeteners and flavours (McCabe et al 1992).

A variety of proteinaceous excipients have been utilized to improve palatability. Various analgesics, hormones, enzymes, antibiotics, vitamins and dietary fibres have been taste masked using prolamine coatings, without impacting on bioavailability. Amiprilose was taste masked by coating with calcium gluconate and sodium alginate; the latter forming a gel on contact with water and effectively masking unpleasant tastes (Nanda et al 2002). A gel-based sweet was developed to improve the taste of paediatric paracetamol (Toraishi et al 1988). Sodium

alginate mixed with ibuprofen and added dropwise to a calcium chloride solution gives a colourless and tasteless gel (Andou et al 1998). The bitter taste of the antibiotic clarithromycin can be taste masked by granulation with carbopol and polyvinyl pyrrolidone (Saleki-Gerhardt & Keske 1997).

Complexation is a well documented approach to taste masking. The palatability of ibuprofen solutions was improved using 1:11 and 1:15 complexes of ibuprofen, hydroxypropyl-β-cyclodextrin and sweeteners (Motola et al 1991). The strong bitter taste of pentoxyverine (carbetapentane) was significantly decreased following complexation (1:1) with cyclodextrins (Kurasumi et al 1991). Similarly, bitter tasting drugs can be complexed with ion exchange resins (Elder 2005). Polystyrene based cation exchange resins (Indion CRP-244 and 254) have been utilized to complex bitter tasting drugs; diphenhydramine, chlorphenamine, ephedrine, noscapine, and amphetamine (Manek & Kamat 1981). The strong cation exchange resin Amberlite IRP-69 can be used to mask the taste of the bitter tasting drugs like paroxetine (Elder et al 2000).

Low solubility salts (dibenzylethylenediamine and bisethylenediamine) of penicillin and the magnesium salt of aspirin are tasteless (Nanda et al 2002). Similarly, the magnesium salts of dihydrocodeine, methylephedrine and chlorphenamine, together with sweeteners, are palatable (Nishikawa & Hyashi 1993).

Dysphagia challenges

The anatomy of the buccal cavity within a paediatric patient is not a scaled down version of that of an adult; and differences exist between neonates and older children, as well as between children and adults. The differences include: the oral cavity is small in a neonate and is completely filled by the tongue; neonates have a set of sucking pads in the cheeks; the soft palate and epiglottis are in contact at rest, providing an additional valve at the back of the oral cavity; the larynx and hyoid cartilage are both higher in the neck and closer to the back of the epiglottis, providing additional protection to the airway; and the eustachian tube runs horizontally from the middle ear to the nasopharynx (rather than the vertical angle found in older children and adults) (Evans-Morris 1998).

Most medicinal products are developed as solid oral dosage forms, typically tablets and capsules (Tuleu 2007); however, more than 25% of adult patients have difficulty in swallowing (dysphagia) these type of medicinal products, and for paediatric and geriatric populations the percentages are much higher. Children over the age of five years can usually swallow a tablet and those as young as three years can be taught, particularly where they suffer from chronic illnesses. Standard tablets (without functional film coats) may be halved (if there is a break-line) or crushed. However, due to difficulties encountered by children with swallowing, alternative formulations, such as oral liquids, oral suspensions, elixirs, drops, dispersible and chewable tablets are often required. Injectable solutions can be dosed orally e.g. phytomenadione injection (Duke & Urquhart 1997).

Other approaches to paediatric formulations

There is a clear need for specific paediatric formulations that permit accurate dosing and enhance compliance by this unique patient group(s). Other paediatric-friendly dosage forms are melt forms, needle-free injections, nasal solutions, nasal drops, eardrops, ear ointments, eye drops and ointments, scalp applications and other dermal applications (creams, ointments, lotions) and powders (nutritional powders, powders for reconstitution, sprinkles, etc.). Suitability for paediatric administration is based on the requirement not to dilute to strength, and that strength matched the dosing instructions (Tan et al 2003). These formulations in turn may require different flavours and colours for different markets, based on cultural preferences. These formulations may require different concentrations from the existing, registered adult formulation, and these differences may go beyond merely prorated differences in mg/kg dosing regimens. There are also age related differences in sensory discrimination of the tongue, sensory discrimination decreasing with increasing age (Aviv et al 1994).

Controlled-release multiparticulate dosage forms offer a distinct advantage over many conventional dosage forms used in paediatric medicine. In addition to their small size helping overcome issues associated with dysphagia, they may be designed to taste mask whilst also modifying the release of the active drug substance from the formulation. Controlled-release dosage forms have the potential to extend the period of time between dosing, reducing the number of doses required per day, enhancing patience compliance and patient/clinician convenience. This is particularly relevant for paediatric patients suffering with chronic conditions which usually require regular dosing by the patient, parent or teacher during the day (Kyngas et al 2000).

Spacer devices can be used in conjunction with nebulized inhalers for delivery of paediatric formulations to the lung. Dry powder devices can usually be used for children aged four years and above, and some devices require very low inspiration flow rates ($30\,L\,min^{-1}$) e.g. Turbohalers, whereas children aged 10 years and above are, after appropriate training, usually able to use an inhaler.

Doses of parenterally delivered drugs can be tailored to a wide range of paediatric patients by adjusting dose volumes. However, this route of administration is still not community-friendly, but the advent of hospital care in the community will facilitate greater uptake. Subcutaneous and intramuscular injections are the most widely used parenteral dosage forms in the community (Duke & Urquhart 1997).

Rectal preparations (for example, suppositories) offer a relatively easy route of administration for certain conditions, for example, seizure control using rectal diazepam; however, compliance may be an issue due to parent or carer distaste for this route of administration.

Dosing devices are intrinsic to the successful dosing of the paediatric medication; e.g. dosing spoons, syringes, etc. Finally, consideration needs to be given to different delivery systems (ICH E11 2000).

Conclusions

It is obvious from this short review that there is a clear need for paediatric medicines; however, there are still some major challenges. The ethics of conducting placebo-controlled paediatric studies is still a matter of great concern and hampers

meaningful investigations in many therapeutic areas. Such ethics are likely to result in a new paradigm of clinical study design protocols.

The different physiological development stages of the various different paediatric sub-group, from neonates to adolescents, pose many challenges to drug therapy. Well characterized drugs in adults can pose serious risks in paediatric populations because of differences in absorption, distribution, metabolism and extraction of the drug.

The regulatory agencies in Europe and the US have made clear strides towards increasing the incentives for industry to develop drugs (and relevant drug products) for paediatric conditions. However, in an increasingly competitive environment it is equally clear that industry does not feel that risk/benefit equation has been adequately addressed. The need to develop off-patent drugs (and relevant drug products) for paediatric conditions is equally important, but less easily realizable because of the poor record of innovative research and development by the generics drug industry. Consistent labelling of therapeutically equivalent generic products is another issue, there being evidence of differences in paediatric dosing advice between generic products.

Palatability and dysphagia remain the two greatest challenges to paediatric drug product development. Neither is trivial and they remain a significant barrier to development of 'child-friendly' dosage forms. A less well documented impediment to paediatric dosage form development is the safety and acceptability (particularly in neonates) of some common excipients. There are unfortunately many examples of adverse events, some fatal, which have occurred after exposure to common excipients. Unsurprisingly, the greatest offenders are antimicrobial preservatives, which are toxic by design and are included in formulations for their ability to be bactericidal and/or bacteriostatic (Elder & Newby, unpublished data). Conversely, the potential for fatal infections by opportunistic pathogens in the absence of preservatives tends to be a much greater hazard and therefore the continued use of preservatives is still supportable. However, there needs to be greater awareness and caution when using preserved formulations in children, and particularly in neonates.

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