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Paediatric formulations—Getting to the heart of the problem

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Abstract

Many medicines prescribed for children are unlicensed. Solid dosage forms present problems as children have difficulty swallowing whole tablets or capsules. When medicines are not licensed for children, it is unlikely that there will be a suitable, licensed liquid formulation and so extemporaneous liquid preparations (prepared at the dispensary or by GMP 'special' manufacturers) are often used. This study looked at a list of medicines commonly prescribed for children with cardiovascular conditions in an English specialist paediatric hospital and classified them according to licensed status and available formulations. As expected, most medicines used for children with cardiovascular problems were unlicensed and where this was the case, usually only 'special' liquids or extemporaneous preparations were available. Problems linked with formulations highlighted in this therapeutic category were: problems in dosing accuracy and unknown bioavailability of extemporaneous products, the use of potentially toxic excipients, and lack of access to modified release preparations for children. These problems are likely to extend to other paediatric therapeutic areas. There is currently a large, unmet need to improve formulations of commonly used paediatric medicines, both through licensing and standardising the production of extemporaneous and 'special' formulations. It is expected that the awaited European regulation will help to meet some of those needs.

Keywords: Cardiovascular drugs; Paediatric medicines; Licensed liquid; Special products; Extemporaneous preparations

1. Introduction

Children are not small adults! Differences in physiology during development mean the way in which they absorb, distribute, metabolise and eliminate drugs cannot be predicted from adult data (Kearns et al., 2003; de Zwart et al., 2004). Children represent a vulnerable group, with parental consent for treatment relying on the evidence-base and expertise drawn upon by professionals caring for them. Before any medicine is authorised for use in adults, the product must have undergone clinical testing to ensure that it is safe, of high quality and effective. This is not the case with all medicines for hospitalised children as, depending

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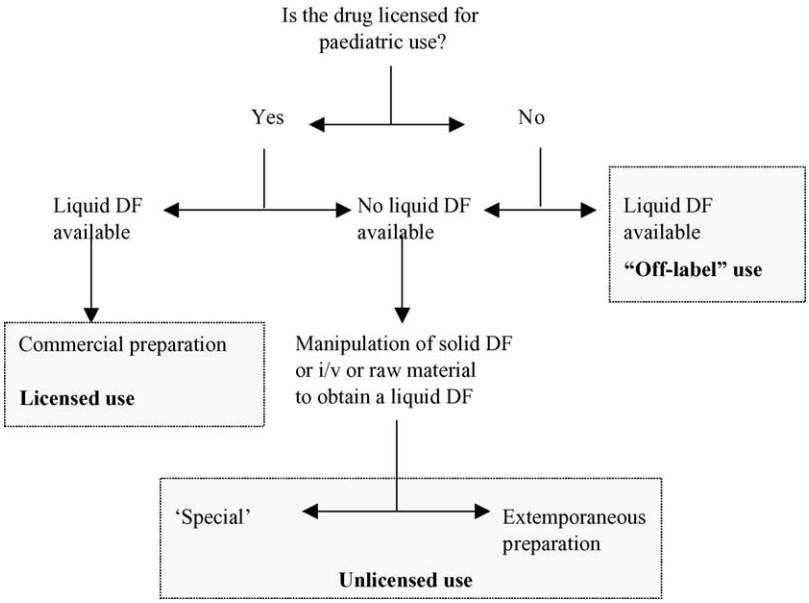

Fig. 1. Decision pathway for providing oral doses to children for whom whole tablets/capsules are unsuitable (DF: dosage form; i/v: intravenous).

on speciality, between 30 and 90% are not licensed for purpose (termed "off label" OL) or have not been licensed at all (termed "unlicensed", UL) (Conroy et al., 2002; Turner et al., 1998). This is also the case in the community but possibly to a lesser extent (Schirm et al., 2003).

Using medicines that are not licensed means there is limited available evidence on safety, quality and efficacy and a potentially increased risk of adverse drug reaction (Choonara and Conroy, 2002; Turner et al., 1999). In addition to a lack of systematically compiled evidence for the use of unlicensed medicines, many are available only as solid dosage forms (Schirm et al., 2003). Depending on age many children are unable to swallow whole tablets or capsules (Michele et al., 2002), even when given specific training (Czyzewski et al., 2000). Furthermore, as dosing is often based on body weight, only a proportion of a solid dosage form has to be given which can be difficult to achieve. Fig. 1 summarises the options available to administer oral medicines to children who cannot swallow whole solid dosage forms. In 2001, an audit at Great Ormond Street Hospital (GOSH) in London (UK), one of seven specialist paediatric hospitals in England, revealed that manipulations such as tablet cutting, tablet crushing and opening capsules was necessary to administer 26% of oral doses given to inpatients (data unpublished). Splitting tablets leads to dose inaccuracy (Breitkreutz et al., 1999; Rosenberg et al., 2002; Teng et al., 2002), crushing tablets can affect absorption (Breitkreutz et al., 1999) and cause therapeutic failure (Notterman et al., 1986).

The aim of this study was to look into the availability of drug formulations used in a paediatric hospital within a single therapeutic area. A recent survey including the seven specialist paediatric hospitals in England, found that many unlicensed chemical entities coming from the BNF "cardiovascular system" category were extemporaneously prepared: 11.1% in terms of the number of drugs and 14.5% of the workload (Yeung et al., 2004), those drugs often being potent and with a narrow therapeutic index. The cardiothoracic unit at GOSH has over 7000 patient attendances per year, and the vast majority of patients will receive cardiovascular medicines. In addition, patients with other underlying conditions may receive such drugs (e.g. patients with hypertension secondary to renal failure). This study aims to reflect on paediatric formulation and licensing problems using medicines that act on the cardiovascular system as an example.

2. Materials and methods

A list of commonly used cardiovascular medicines prescribed at GOSH was drawn up. The drugs were classified according to the available formulation and their licensed status. They were qualitatively classified into two categories:

- If a licensed liquid dosage form was available.
- If no licensed liquid dosage form was available. In that case, the way the doses could be administered was further investigated and reported as 'special' or 'extemporaneous preparation'.

The term 'special' defined an extemporaneous non-sterile liquid preparation produced under good manufacturing practice (GMP) conditions by a specials manufacturer, which includes suitably licensed hospitals units. Companies are allowed to supply unlicensed medicinal products formulated in accordance with the requirement of a doctor ('named patient supply') if they hold a manufacturer's (specials) license issued by the Medicine and Healthcare Products Regulatory Agency (MHRA). Extemporaneous non-sterile liquid oral preparations are prepared mainly from manipulated solid dosage forms; either by the carers or hospital or community pharmacies. They can also be prepared by dilution of an existing liquid dosage form (e.g. injection).

3. Results

Table 1 lists oral cardiovascular drugs commonly used in children for which a licensed liquid is available in UK. Table 2 lists the medicines for which there is no licensed liquid available in UK. Fig. 1 summarises the options available to administer oral medicines to children.

The majority of medicines used for children, which act on the cardiovascular system, were unlicensed. There was no licensed liquid form for most medicines although 'special' preparations were available for almost all. However, most 'special' liquids are expensive and have short shelf-lives, which mean that extemporaneous production still often occurs. A wide range of paediatric formulation strengths were available, which adds to the complexity of prescribing and administering the drugs.

4. Discussion

There is evidence suggesting that adverse drug reactions are more likely with UL/OL medicines (Turner et al., 1999; Choonara and Conroy, 2002). Dosing errors are thought to be a major route by which children are exposed to medication errors (Wong et al., 2004), and many of these could be linked to the use of high-strength adult formulations.

4.1. What is wrong with the available liquid formulations?

Licensed liquid formulations of drugs (Table 1) are, for obvious reasons, the best option: their efficacy is supported by clinical trial data, the dose is easy to adapt to weight or body surface area, there are fewer problems with swallowing, and prescribing information is easily available. Nevertheless, the taste of the drug or the preparation itself is crucial to achieve good compliance, especially in a field such as cardiology where medicines are used to treat long-standing conditions.

Table 1
Commonly used cardiovascular drugs for which a licensed liquid is available in UK

Drug	Paediatric license	Description	Remarks
Amiloride	Yes	Sugar-free oral solution	Contains propylene glycol
Atenolol	No	Syrup	Commercial preparation licensed for adults. Not recommended for use in children by manufacturer.
Digoxin	Yes	Elixir	Contains ethanol and propylene glycol
Flecainide	Yes	Syrup	Drug licensed for children over 12 years old
Furosemide	Yes	Sugar-free oral solution	Range of strengths available. All strengths contain ethanol and propylene glycol
Propranolol	Yes	Sugar-free oral solution	Contains propylene glycol

Table 2
Commonly used cardiovascular drugs for which no licensed liquid is available in UK

Drug	Paediatric license	Special available	Remarks
Amiodarone	No	Yes (suspension)	Drug sparingly soluble in water. Special only has 1-month shelf-life. Extemporaneous preparation can be made (suspension from tablets)
Amlodipine	No	Yes (suspension)	Drug sparingly soluble in water. Special only has 1-month shelf-life. Crushed tablets suspended in water often used
Aspirin	No	No	Very water soluble drug—use dispersible tablets
Bosentan	No	No	Crushed tablets suspended in water—very expensive
Captopril	No	Yes (solution and 2 mg tablets)	Solution—must be refrigerated, only 1-month shelf-life. Licensed solution in Australia, packed under nitrogen with only 1-month shelf-life once opened. Easy dispersible low strength tablets crushed and mixed in water (these have recently been withdrawn from the market)
Carvedilol	No	Yes (suspension)	Drug sparingly soluble in water. Special only has 1-month shelf-life. Crushed tablets suspended in water often used
Clonidine	No	Yes	Dilution in water of the injection is often used, must be refrigerated. Special has a 1-month shelf-life
Enalapril	No	Yes (suspension)	Drug sparingly soluble in water. Crushed tablets suspended in water often used
Hydralazine	No	Yes (soluble tablets)	Soluble tablets available. The injection can be diluted and used orally and kept 24 h at room temperature
Nadolol	No	Yes (suspension)	Drug sparingly soluble in water. Special only has 1-month shelf-life. Crushed tablets suspended in water often used. Low strength tablets recently withdrawn in UK
Nifedipine	No	No	Drops in macrogol 200 can be imported—Crushed modified release tablets or removal of nifedipine liquid from soft capsules used
Pravastatin	No	Yes	Drug freely soluble in water, crushed tablets often dissolved in water. Special has 1-month shelf-life
Prazosin	Yes (>12 years old)	No	Manipulated solid oral dosage form suspended in water
Ramipril	No	Yes (suspension)	Drug sparingly soluble in water. Crushed tablets suspended in water often used. Special only has 1-month shelf-life
Sildenafil	No	No	Crushed tablets suspended in water—expensive
Spironolactone	No	Yes	Large range of strengths available
Warfarin	No	Yes	Drug freely soluble in water, crushed tablets often dissolved in water. Special only has 1-month shelf-life

Excipients are often required to modify the olfactive properties of liquid preparations (colouring, sweetening and flavouring agents). The choice of natural versus artificial sweeteners (e.g. syrup versus sugar free SF preparations, Table 1) is polemical: the relevance of animal studies demonstrating the carcinogenic potential of saccharin and cyclamate is unclear, whereas monosaccharides (sorbitol, mannitol) may contribute to osmotic diarrhoea. Some sweeteners may cause dental caries or poor control of diabetes mellitus (sucrose, dextrose).

The use of excipients is also essential for ensuring dose uniformity if the drug is in suspension, to promote chemical stability, and prevent microbial growth during storage and use. Formulating stable liquid medicines often requires substantially more excipient content compared with solid dosage forms. Unlike active ingredients, excipients are not well regulated in most countries and some can be harmful to children (Bigeard, 2000; Pawar and Kumar, 2002; Rabiu et al., 2004). Propylene glycol is considered less toxic than other glycols, but is estimated to be one-third as intoxicating as ethanol. In the past, its administration in significant volume was associated with adverse effects on the central nervous system (Arulanantham and Genel, 1978), especially in neonates and children. Nevertheless, licensed commercial preparations containing propylene glycol (amiloride, propranolol, Table 1) and some also

containing ethanol (digoxin, furosemide, Table 1), and ethanol as a solubilising agent, were still found.

The formulator is left with a difficult choice over excipients, either those for which toxicity is known and therefore predictable, or those with safety profiles which have not been established in children.

Interestingly, although there is a licensed liquid preparation of atenolol (Table 1), it is unlicensed in children. This means that although it can be expected to be chemically stable and bioavailable in adults, no evidence has been reviewed by the MHRA to show whether it is safe, or indeed effective, when used in children. This was the only example of a licensed liquid formulation which is not recommended for children.

Both licensed and unlicensed preparations are often produced in several different strengths. Furosemide is licensed as 20 mg/5 mL, 40 mg/5 mL and 50 mg/5 mL. Some hospitals chose just to stock the 50 mg/5 mL strength in order to reduce the risk of medication errors, but this may mean that a small child of 3 kg will require a dose of 0.3 mL, which is difficult to measure accurately. The range of strengths for 'special' products is also extremely diverse as manufacturers will produce various strengths by request. An error where a child was given a 10-fold overdose of spironolactone (Table 2) was discovered (Anonymous, 2003) when the hospital pharmacy supplied 1 mg/mL and the community pharmacy supplied 10 mg/mL suspensions. Whilst the availability of different strengths could be seen as an opportunity to get the most appropriate dose, where there is a 10-fold difference in available strengths, confusion and serious dosing errors can occur (Koren et al., 1986).

The use of 'special' liquids compared to extemporaneous preparation, reduces the risk of production errors and increases the quality of the medicine as manufacturers adhere to quality assurance systems such as batch tracking, record keeping, GMP, adverse reaction reporting, and inspections by legal authorities at regular intervals, as for licensed liquids. Despite this, there are a number of factors hindering the wholesale adoption of specials. These include short shelf-life (e.g. amiodarone has a 1 month shelf-life, captopril has to be kept refrigerated for 1 month only, Table 2) leading to frequent ordering, wastage and increased cost along with the lack of immediate availability for rare products or for patients living far away from the specialist centres. Yeung et al. (2004) surveyed English specialist paediatric hospitals and showed that more than 50% of the extemporaneous preparations made in UK were available as specials. This also reflects on the lack of standardisation in medicines management across UK due to a lack of official guidance and information on 'specials' making supplies difficult, especially for non-specialist centres. Difficulties arising from this lack of national guidance are further amplified by the restrictions on advertising 'specials' making it difficult to find out whether a product is available. Due to their legal status, manufacturers are not allowed to promote their product in any way as 'specials' lack the regulatory approval from clinical trials on dosing, efficacy and safety. The fact that the pharmacokinetics and pharmacodynamics of 'special' products are rarely studied remains their largest disadvantage compared with licensed products.

4.2. What is wrong with extemporaneous dispensing of liquids?

In order to provide liquid formulations to administer drugs with no liquid preparation available, or to overcome 'special' supply problems, extemporaneous formulations are needed. They can be prepared by dilution of existing liquid dosage forms (e.g. dilution of the injectable form of clonidine, Table 2) if formulation parameters such as excipients and pH are suitable orally; they can be prepared directly from raw materials/chemicals although there was no example in the cardiovascular therapeutic area. The procedure of crushing tablets and "dispensing/suspending" in water, food or beverages prior to administration is associated with the highest risk of errors in extemporaneous dispensing, mainly because they are difficult to track as there is no record or control of preparation.

Extemporaneous preparations tend to have little or no compatibility study back up. Very few well-controlled stability studies are published on in vitro compatibility issues between manipulated solid dosage forms and food/beverages. Studies have been undertaken with drugs for the gastrointestinal system (Johnson et al., 2003; Carrier et al., 2004), 5HT3 antagonist drugs (Yamreudeewong et al., 1995) and labetalol for the cardiovascular system (Nahata, 1991). Standardisation of recommendations for suitable alimentary vehicles is highly problematic. For example, a

manufacturer may recommend that the drug is stable when tablets are dissolved in apple juice (Imatinib SPC, 2004), but surely it cannot be known whether the drug is stable in any apple juice or other juices, whose pH and ingredients may vary significantly between manufacturers and countries.

There are few stability studies undertaken on extemporaneous products. In the literature, shelf-life is determined by chemical stability, mainly assessed by HPLC, for specials or some extemporaneous preparations formulated in pharmaceutical vehicles. Vehicles can be commercially available (e.g. Ora®plus, Ora®sweet, Keltrol®) or prepared in the dispensary (e.g. methylcellulose 1%, syrup NF). Mostly, stability testing does not include physical and microbial stability testing and does not mimic the 'in-use' stability when the preparation encounters variable temperatures and frequent opening during the treatment course.

The bioavailability of extemporaneous products can be unpredictable. A gross formulation obtained from crushed solid dosage forms may not be bioequivalent with the dose form swallowed whole. In the past, the priority has been to provide a formulation that children can take rather than a formulation with optimised bioavailability. Notterman et al. (1986) described an example of inadequate isoniazid bioavailability of crushed tablets and an extemporaneous preparation made from the injection, compared with a licensed liquid.

As mentioned in Table 2, drug solubility is very important to consider in extemporaneous preparation. If the active is not soluble, it can lead to inaccuracy of dosing through a lack of dose uniformity and reproducibility. This is a major consideration when no suspending agents are used, especially when the person administering the dose is inexperienced and the dose is small (Tuleu et al., in press).

Other problems with extemporaneous dispensing include the expense of some drugs (bosentan, sildenafil, Table 2) and the consequences of production errors, which can be fatal (Anonymous, 2000).

4.3. Is dosing accuracy a problem?

Where 'special' products are used, there is some degree of certainty that the drug will be present in the stated quantity within the expiry period. The main difference between 'specials' and licensed liquids is that their bioavailability usually remains untested. This means that the bioavailability of 'specials' may depend on the manufacturing technique used and may differ between manufacturers. There is little incentive for 'specials' manufacturers to perform bioavailability/bioequivalence studies as, without going to the considerable expense of attempting to license the drug, dosing recommendations based on such studies cannot be legally made.

Extemporaneous preparation of doses by nurses or carers is probably the least accurate method. The weight of a split tablet can range from 50 to 150% of the actual half-tablet weight (Teng et al., 2002) and accuracy does not seem to be improved by using commercially available tablet cutters (Breitkreutz et al., 1999). Insoluble drugs are often crushed and dispersed in water to give a proportion of the dose. Without the use of suspending agents, this method provides highly variable dosing especially if the dose (volume) is small.

Although drug dosing in children is often based on body weight, this can be a poor predictor of drug clearance (Anderson et al., 1997). It is therefore questionable how much impact inaccurate dosing will have on clinical outcomes, especially with anti-hypertensive medications where dose is titrated to response. The main problem will be with variability in dosing, which occurs most frequently when solid doses are manipulated immediately prior to administration.

Warfarin is available as a special but the expense and short shelf-life along with the drug's water solubility means that it is usually administered as tablets crushed and dispersed in water. In a cohort study of paediatric patients receiving warfarin therapy, children under 1 year took significantly longer to achieve the target international normalised ratio (INR), needed more INR tests per month and required more dose changes per month compared with other age groups. Children under 6 years were more likely to have INRs below the target range (Streif et al., 1999). There are many factors which could explain these differences but one which the authors did not explore was formulation. Unfortunately, no details on the drug formulation were given but it would seem most likely that crushed tablets were used to administer the dose to younger age groups. Using an inappropriate formulation leading to inaccurate dosing could have been a factor in

these patients requiring more blood tests (potentially traumatic finger/heel pricks) and failing to reach target INR values as quickly. This example highlights the potential problems encountered when narrow therapeutic index drugs are not available in liquid formulations showing that in such situations, dosing accuracy is a problem.

4.4. Do children need access to modified release products?

Nifedipine is unlicensed for use in children but is often prescribed for hypertension secondary to renal failure. In adults, short acting nifedipine is not recommended for use in hypertension due to the rapid drops in blood pressure it causes, leading to complications, such as reflex tachycardias (British National Formulary, 2005). The usual recommendation is to give a modified release (m/r) preparation to obviate large changes in blood pressure. However, the only available m/r nifedipine preparations are in tablet form, and many children are unable to swallow whole tablets (Czyzewski et al., 2000). As a result, children are prescribed short-acting nifedipine preparations, which include withdrawing the dose from soft capsules, crushing m/r tablets and using imported drops which have proved to give variable dosing (Tuleu et al., in press). There is little evidence for the safety of using short-acting nifedipine in children, but a retrospective review did find it effective in producing large reductions in mean arterial blood pressure, albeit giving little information about how doses below 10 mg were extracted from the capsules (Blaszak et al., 2001). Serious adverse effects of large decreases in blood pressure in children can include cerebral ischaemia (Sasaki et al., 1997), particularly when the patient has long-standing hypertension. This, along with a lack of prospectively collected safety data, is the reason that some paediatricians advise against the use of short-acting nifedipine outside the specialist hospital environment (Flynn, 2002).

Nifedipine provides a prime example of the disparity which exists between medicines for children and adults. Licensing of nifedipine affords adults the benefit of once daily dosing, decreased risk of adverse effects and formalised post-marketing surveillance. Children, treated with the same drug, have to take the dose three times a day, and are placed at potentially increased risk of adverse effects because no m/r formulation is available. So, in answer to the question: do children need access to modified release products, the answer is yes; the challenge being to develop innovative drug delivery methods that children are able to take. Such strategies may include: m/r small platforms (minitablets, minicapsules), trans-dermal delivery (especially for neonates), m/r liquids (nano or microparticles) with suitable polymers.

4.5. Why have formulation issues not been addressed in the past?

Drug formulation issues are frequently overlooked in the reports of paediatric clinical trials. One of the core principles in reporting scientific research is to give full details on how the experiment was carried out so that it can be repeated. Clinical trials involving medicines in children routinely fail to do this by omitting information on the drug formulation and how it was administered, impairing the reliability and validity of results and hindering the transferability into clinical practice. In the previous two sections, published trials on nifedipine (Blaszak et al., 2001) and warfarin (Streif et al., 1999) have been mentioned, neither of which gave full details of the formulation used and how the drug was administered. A study on the use of amlodipine in children with hypertension described how they were administered a weight-specific dose using a powder prepared from crushed tablets (Tallian et al., 1999). The report did not specify how the powder was administered. It is unlikely that each dose of powder was individually weighed out and as amlodipine is only sparingly soluble in water, dispersing the dose in water without using a suspending agent will lead to variable dosing. Another study (Flynn et al., 2000) on amlodipine in children recognised this problem by using a suspension formulated in the hospital pharmacy.

These studies represent the variability of formulation and administration information provided in published paediatric clinical trials. The problem is not isolated to cardiology medicines (Standing and Wong, 2004). A review of recent paediatric clinical trials in high impact factor journals (Standing et al., in press) found adequate formulation information is provided in only 37% of reports. Adequate formulation reporting was classified as providing sufficient information for the study to be repeated (formulation and manufacturer

stated, where formulation was a tablet/capsule, an account of whether children were able to swallow the dose whole or how an aliquot of the dose was administered). Especially in the case of 'special' or extemporaneous preparations, it is vital that a reference on the medicine's formulation is given, as unlike licensed products, unlicensed preparations may not be bioequivalent between different manufacturers (or between batches). This result suggests that many authors and journal editors do not consider providing formulation information in paediatric clinical trials to be important, when its potential impact on the amount of drug received may have a profoundly negative effect on the reproducibility (reliability) and to a lesser extent validity of the results.

In addition to clinical trials frequently not providing formulation information, therapeutic failure can often have a number of explanations. For example, the failure of amiodarone to control a patient's arrhythmia may be due to a dosing with a proportion of a crushed tablet dispersed in water. Many drugs are sparingly soluble such as amiodarone, nifedipine, in water, in abscence of a suspending agent, most of the drug will be in the solid form at the bottom of the measuring device. Unless the mixture is thoroughly stirred immediately prior to giving the dose, the amount of drug received by the patient is likely to be very erratic (Tuleu et al., in press). 'Special' and extemporaneous products have almost never been tested for bioavailability and so patients may be under or over dosed compared with a level expected to be achieved by extrapolation data from licensed formulations in adults. It is therefore possible that therapeutic failure or adverse reactions due to overdose resulting from inappropriate formulations go unrecognised by paediatricians and pharmacists caring for the patient.

Another important reason for inadequate formulation availability for children is a commercial one. At present in UK, there is no financial incentive for pharmaceutical companies to license paediatric medicines and develop suitable formulations due to the relatively small market and high cost of developing and producing them.

4.6. Will formulations improve in the future?

In September 2004, the European Commission adopted a legislative framework for regulation of medicinal products for paediatric use in order to work towards an ethical, effective and favourable environment for paediatric research and development (Medicines for Children, 2004). These arrangements are similar to the one established in USA during the late 1990s. The key objectives of the EU proposed regulation are to increase the development and authorisation of paediatric medicines while ensuring they are subject to high quality research, but that no unnecessary clinical trials are carried out. The proposal also aims to improve the information available on medicines for children. Key elements in the proposal are:

- A new expert committee within the European Medicines Agency (EMEA) to assess and agree Paediatric Investigation Plans (PIPs) presented by the pharmaceutical industry. A system of free scientific advice will also be provided by the EMEA.
- A requirement at the time of marketing authorisation application that data is presented on the drug's use in children. A system of waivers and deferrals will ensure the requirements do not delay the authorisation for medicines in adults.
- A reward for studying medicines for children of 6 months extension to the supplementary protection certificate; in effect, 6-month patent extension for the product (including adult use).
- For off-patent medicines, 8 plus 2 years of data exclusivity on paediatric use of the product for new studies awarded via a Paediatric Use Marketing Authorisation (PUMA). These incentives are very similar to those in USA but the EU proposal is more robust as it requires the sponsor to market the paediatric medicine for the approved indication within 12 months, speeding up the availability for patients. It does not distinguish between studies required (with claimed benefit to children) and those requested (with potential benefit to children) as in USA.
- Increased safety monitoring for children's medicines (pharmacovigilance).
- A compulsory submission by industry of existing studies in children, an inventory of the EU therapeutic needs of children and an EU network of investigators and trial centres to conduct studies required. The EU proposes a transparent approach to negative outcomes of the trials in children as any results (positive or negative) will be included in a database of ongoing or terminated studies; the

results will also be incorporated on the drug label, regardless of whether the indication is approved or not.

This awaited legislation is likely to become effective late 2006 and it is hoped that all future medicines for children will have been investigated in children and, where there is an appropriate indication, a licensed paediatric formulation will be produced.

However, delays are anticipated as the Medicines Investigation for the Children in Europe (MICE) fund, equivalent to the National Institute of Health and FDA set up to support old and commercially disregarded drugs in USA, has not yet been sourced. This is a real issue as generics manufacturers do not have substantial resources for research and development beyond equivalence studies.

In the meantime, extemporaneous preparation, be it at the bedside, by pharmacists or 'special' manufacturers will continue to be a major route by which paediatric oral medicines are prepared. As a result of strong national concern in UK (Safer and Better medicines for children, 2004; National Service Framework (Standard 10), 2004), the first edition of the British National Formulary for Children (BNF-C) is due to be published (British National Formulary for children, 2005). It will provide a practical, relevant, authoritative information source and guide prescribing, dispensing and administration of medicines to children up to 18 years of age. By reflecting current evidence on efficacy and safety of drugs within the limits of available clinical trial data, BNF-C will provide practical guidance on the 'off label' use of medicines.

In addition to legislative and formulary developments, innovations in pharmaceutical formulations should improve the ease in which children can access medicines. Innovative m/r preparations have previously been mentioned, and the following areas are also ripe for future developments and research:

- New routes of administration such as oral-transmusosal (buccal strips), intra-nasal and transdermal (for neonates mainly).
- More research into alternative safe excipients for children such as natural polymers (e.g. cyclodextrin to mask taste of drugs, improve solubility or protect drugs/patient).
- Children's ability to swallow and their preferences need to be investigated. This will direct future formulation research towards (mini) tablets, chewable tablets, dispersible tablets or more oral liquids.

Although new and innovative formulations are urgently needed, work on extemporaneous formulation should not be disregarded.

Those findings reflect on numerous problems associated with the lack of suitable formulations for children. This emphasised the difficulty in prescribing and administering cardiovascular drugs as a proof of concept, which can be extended to many other therapeutic areas. In an era of evidence-based medicine, it is unacceptable that drug formulations given to children are not better designed to provide accurate and reproducible dosing. With the expected new European regulations and the obligation of clinical testing on the paediatric population, it will be important that a strategy for paediatric formulation research is put in place. The future of paediatric drug formulations seems bright, but legislation must be supported by innovative research on new and existing delivery methods.

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