Establishing a baseline for the monitoring of medicines availability for children in the UK: 1998–2002

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Aim

To determine changes in the availability, in terms of licensing and formulations, of medicines for children in the UK between 1998 and 2002.

Methods

Using the Association of British Pharmaceutical Industry (ABPI) Compendium of Data Sheets and Summaries of Product Characteristics (SPC) 1998 and the Medicines Compendium 2002, licensed medicines available in the UK in the calendar years 1998 and 2002 were examined.

Results

In 1998, 61% of chemical entities/fixed-dose combinations were licensed in some form for children compared with 64% in 2002. Of the chemical entities/fixed-dose combinations with oral formulations, 250 (33%) in 1998 had an oral formulation suitable for use by children and in 2002 there were 284 (34%). Of the 129 new chemical entities registered in the UK between 1998 and 2002, only 30 (23%) were licensed for under the age of 12 years and 19 (15%) for the neonatal age group. A total of 480 medicines licensed for children were withdrawn from marketing but only cisapride and primidone had no generic or therapeutic alternatives.

Conclusion

Although there was improvement in the availability of medicines for children in the UK over the 5-year period (1998–2002), considerable inequities still existed between children and adults.

Introduction

There are three key requirements of access to medicines: access to the chemical entity, access to a suitable formulation and information on appropriate dosing, indications and potential adverse events. The system of licensing (Market Authorization) of medicines has been designed to ensure the quality of medicines and also to ensure their efficacy and safety. However, this system also allows particular groups to be excluded from the licence. Hence, many of the medicines licensed in the UK do not have approval for marketing to the paediatric age groups, although the extent of this phenomenon is

unknown. In order for medical practitioners to treat children with these medicines they are obliged to prescribe them 'off label' (i.e. use medicines outside the indications for which they have Marketing Authorization) or unlicensed (where a medicine does not have a Marketing Authorization).

In the UK, 36% of children received at least one drug that was either unlicensed or off label during their inpatient stay on general paediatric surgical and medical wards [1]. In a paediatric intensive care setting 70%, and in a neonatal intensive care setting 90%, of patients received at least one medicine on either an off-label or

unlicensed basis [2, 3]. These rates were similar to other European countries and did not indicate a phenomenon unique to the UK [4]. This may increase the risk of an adverse drug reaction in children since it has been shown that adverse drug reactions are prominent with unlicensed and off-label drug use in paediatrics [5].

A limiting factor for a child's access to medicines is the suitability of the formulation. A large number of drugs are in a formulation that is unsuitable for use in infants and children, i.e. not in liquid dosage form or other forms suitable for children [6]. Liquid dosage forms allow flexible dosing where precise tailoring of dose to body weight is critical. When a drug that is only available in an unsuitable oral dosage form is prescribed, tablets are crushed or capsule contents are mixed with solid food or with a palatable drink. In this case, the active ingredient is diluted and could potentially result in delivery of incomplete doses or errors in dosage preparation. Alternatively, extemporaneous formulations may be dispensed, with unknown qualities of stability, solubility, bioavailability, toxicity and palatability [7–9]. As a consequence, infants and young children are particularly disadvantaged [10].

The range of medicines marketed within a regulatory domain changes over time as new drugs are introduced and older, less-used drugs and formulations are withdrawn from the market. Although there is published information about the paediatric licensing status of drugs introduced in the European Union over the time period 1995–2001, there is limited information about formulations of new chemical entities or about medicines that have been withdrawn over this period [11, 12]. Some of these withdrawn drugs may have been of particular value to the paediatric age groups. A comparison of the range of medicines available, their paediatric licensing status and suitability of formulation for children over a 5-year period should allow such changes to be examined.

The aims of the present study were to determine the changes in the availability of medicines and chemical entities/fixed-dose combinations for children in the UK from the years 1998 to 2002, to identify the proportions of suitable formulations licensed for children in those years and to determine the licensing status of newly introduced chemical entities by age category.

Methods

Licensed medicines available in the UK between 1998 and June 2002 were examined using the Compendium of Data Sheets and Summaries of Product Characteristics (SPC) 1998 and the Medicines Compendium 2002 compiled by the Association of the British Pharmaceu-

tical Industry (ABPI) [13–15]. The Medicines Compendium/ABPI Compendium have been published annually since 1977. The conditions of publication had not changed between 1998 and 2002. An electronic version (eMC) was introduced in 2002 in addition to the hard-copy version. Currently, pharmaceutical companies participating in the eMC select which of their SPCs they wish to have included within the hard-copy Compendium and the data are extracted directly from the eMC on 30 September each year. Participation is not restricted to ABPI members, and both branded products and generics are listed.

The CD-ROM version of the 2002 ABPI Compendium (eMC) was used in addition to the print version of the 2002 ABPI Compendium to examine all medicines that were available in 2002. For the purposes of the study, a medicine was defined as an entry in the Medicines Compendium and therefore represents a drug product, i.e. a manufactured drug product, either branded or generic. Each form and strength was recorded as a separate entry. Information from the compendium was tabulated according to the following categories: brand names, active ingredients, indications, types of formulations, legal category, adult and paediatric dosing information and whether there was a dosage recommendation for children. The data were collapsed down by chemical entity/fixed-dose combination to determine the 'best case' availability regarding suitability of formulations for children and paediatric licensing status. Analyses were performed separately for all medicines and for chemical entity/fixed-dose combinations.

All medicines that were licensed were classified as either injectable, i.e. infusions, intravenous and intramuscular injections; dermal, i.e. medicines that are applied topically (including transdermal patches); vaginal, i.e. pessaries, vaginal inserts; ears/eyes, i.e. ophthalmic solution, aural ointment; inhalation/inhalers; rectal, i.e. enemas, suppositories; nasal, i.e. topical or aerosolized nasal medication; suitable oral (included liquid, powder, oral spray and soluble tablets); or unsuitable oral (including tablets and capsules and other preparations). For the purposes of the study Suitable Paediatric Formulations (SPF) were defined as all formulations excepting unsuitable oral formulations, and therefore represent formulations that can be administered to a young child. Medicines were also classified as General Sales List, Pharmacy Only, Prescription Only Medication (POM) and Controlled Drug (CD) in accordance with the legal status of the medicine.

A comparison was made between 1998 and 2002 to determine any changes in the availability of individual medicines. New chemical entities/fixed-dose combina-

tions licensed between 1998 and 2002 were identified, and their licensing by age category. Age categories were defined using the International Conference on Harmonization's classification: term newborn infants (0–27 days); infants and toddlers (28 days to 23 months); children (2–11 years); and adolescents (12–16/18 years) [16]. Withdrawn medicines were identified and a search was performed in the Excel spreadsheet for generic/therapeutic alternatives that were licensed in 2002. The British National Formulary (BNF), March 2002 issue, was also searched for those medications available in 1998 but with no alternative listed in the 2002 Medicines Compendium.

Results

In 1998 there were 1258 chemical entities/fixed-dose combinations that were registered for marketing in the UK and listed in the Compendium of Data Sheets and 774 (62%) were licensed in some form for children. Of the 693 chemical entities/fixed-dose combinations registered in 1998 with oral formulations, 232 (33%) had an oral formulation suitable for use by children. Of these suitable oral formulations, 190 (82%) were also licensed for use in children. In 2002 there were 1411 chemical entities/fixed-dose combinations that were registered for marketing in the UK and listed in the Medicines Compendium and 917 (65%) were licensed in some form for children. Of the 770 chemical entities/fixed-dose combinations registered in 2002 with oral formulations, 270 (35%) had an oral formulation suitable for use by children. Of these suitable oral formulations, 239 (84%) were also licensed for use in children. There were 1006

chemical entities/fixed-dose combinations available as POM or CD in 1998, 564 (56%) of which were licensed for children and 670 (66%) had a formulation suitable for children. There were 1069 chemical entities/fixed-dose combinations available as POM or CD in 2002, 606 (57%) of which were licensed for children and 713 (67%) had a formulation suitable for children.

In comparison with 1998, there was an increase in the number of medicines available and listed in the Medicines Compendium in 2002, from 3549 to 3913. There was also an increase in the number of medicines licensed for children: 2016 (57%) in 1998 compared with 2290 (59%) in 2002 (Table 1). There was a 13% increase in the number of medicines in a SPF, but little change in the proportion of total medicines available in a SPF: 2097 (59%) in 1998 and 2365 (60%) in 2002. Similarly, there was an increase in the number and the proportion of SPF licensed for children: 1419 (40%) in 1998 and 1639 (42%) in 2002 (Figure 1). However, a large proportion of oral medicines [1452 (80%) in 1998 and 1548 (78%) in 2002] had no suitable oral formulation for children. In addition, the numbers of unsuitable oral formulations licensed for children [597 (33%) in 1998 and 651 (33%) in 2002] were higher than the number of suitable oral formulations licensed for children [313 (17%) in 1998 and 364 (18%) in 2002] (Figure 2).

Of the 129 new chemical entities registered in the UK between 1998 and 2002, only 30 (23%) were licensed for children aged 2–11 years (Table 2). Slightly over half this number, 19 (15%), were licensed for the neonatal age group. Although many of these medicines may

Table 1

Medicines licensed for children in the UK 1998 and 2002

	All licensed medicines, <i>n</i>	1998 Medicines licensed for children, <i>n</i> (%)	All licensed medicines, <i>n</i>	2002 Medicines licensed for children, <i>n</i> (%)
Injectable	891	577 (64.8)	994	639 (64.3)
Dermal	447	285 (63.8)	526	362 (68.8)
Ears/eyes	132	93 (70.5)	144	103 (71.5)
Inhalation/inhalers	119	84 (70.6)	121	98 (81.0)
Nasal	27	20 (74.1)	27	19 (70.4)
Vaginal	42	6 (14.3)	43	6 (14.0)
Rectal	70	42 (60.0)	78	48 (61.5)
Suitable oral	369	312 (84.6)	432	364 (84.3)
Unsuitable oral	1452	597 (41.1)	1548	651 (42.1)
Suitable formulations for children	2097	1419 (67.7)	2365	1639 (69.3)
Total medicines	3549	2016 (56.8)	3913	2290 (58.5)

All medicines licensed and suitable for children in the UK in 1998 and 2002

Figure 1

Licensing and suitability of medicines for children in the UK 1998 (□) and 2002 (■)

Oral formulations licensed and suitable for children in the UK in 1998 and 2002

Figure 2

Licensing and suitability of oral formulations for children in the UK 1998 (□) and 2002 (■)

not be of use in children, anti-infectives as a group would be expected to have general applicability to the paediatric age groups. Of new anti-infectives, five (45%) were licensed for use in children under the age of 12 years, and one (9%) was licensed for use in the neonatal age group. Seventy-eight (60%) of the new chemical entities were in formulations suitable for children, including six with suitable oral formulations, compared with 51 (40%) unsuitable oral formulations.

A total of 480 medicines licensed for children in 1998 were no longer listed in the 2002 Medicines Compendium in 2002. Of the 480, there were generic alternatives (therapeutic equivalents) for 293 and therapeutic alternatives for 185. Seven medicines had no generic or therapeutic alternative: cisapride, methylene blue

trihydrate, primidone, sodium hyaluronate, bacillus Calmette–Guérin (BCG), tuberculin and yellow fever vaccine. BCG, tuberculin, and yellow fever vaccine continued to be available through Health Authorities and Yellow Fever Vaccination Centres. Sodium hyaluronate and methylene blue were listed in the BNF as available from suppliers, but these were not listed in the Medicines Compendium. Although primidone has therapeutic alternatives, there is a subset of patients with intractable seizures for whom this medication would be preferred.

Discussion

Despite improvement in the number and percentage of chemical entities and medicines licensed for children,

Table 2New chemical entities, licensing by age group, *n* (%)

Therapeutic category	Total	0–27 days	28 days to 23 months	2–11 years	12–16/18 years
Nervous system	18	0 (0.0)	0 (0.0)	1 (5.6)	6 (33.3)
Contrast media	18	12 (66.7)	12 (66.7)	14 (77.8)	14 (77.8)
Oncology and immunology	17	0 (0.0)	0 (0.0)	1 (5.9)	3 (17.6)
Hyperlipidaemia/blood disorders	14	3 (21.4)	3 (21.4)	3 (21.4)	6 (42.8)
Alimentary tract and metabolism	12	1 (8.3)	1 (8.3)	1 (8.3)	1 (8.3)
Anti-infectives	11	1 (9.1)	1 (9.1)	5 (45.4)	8 (72.7)
Genitourinary	7	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diagnostic agents	6	2 (33.3)	2 (33.3)	3 (50.0)	4 (66.7)
Eye/ear	6	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Cardiology	6	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal	5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory and allergy	4	0 (0.0)	0 (0.0)	0 (0.0)	4 (100.0)
Dermatology	3	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)
Endocrine/hormone	2	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)
All categories	129	19 (14.7)	19 (14.7)	30 (23.2)	49 (38.0)

the inequities between the availability of medicines for children, compared with that for adults, persisted over the course of the study. The percentage of chemical entities/fixed-dose combinations licensed for children in the UK, and the percentage of orally administered medicines with formulations suitable for children, both increased. In addition, the percentage of oral formulations that were suitable for children increased by a few percentage points. However, around one-third of the POM or CD chemical entities/fixed-dose combinations were not easily accessible to children because of the lack of suitable formulations and >40% were not licensed for use in children.

The availability of medicines for children in the UK compares favourably with other regulatory domains. The proportion of medicines licensed for children in the UK in 2002 (58%) compares favourably with that of Australia (38%) or New Zealand (35%) [17, 18]. In addition, within the UK over the 5 years there was a slight improvement noted in the proportion of medicines licensed for use in children, from 56.8% in 1998 to 58.5% in 2002, and a net increase in the number of medicines available for children in 2002 of 274. There were an additional 268 medicines with formulations suitable for children, compared with an increase of 106 in Australia and a decline of 53 in New Zealand. The proportion of suitable formulations licensed for paediatric use in the UK (41.9%) in 2002 was markedly higher than that found in New Zealand (24%) and in Australia (25%).

The present study indicates an ongoing discrepancy between the licensing of new chemical entities for children and for adults. This has also been described in previous papers. Of the 127 active substances and 14 vaccines granted a community marketing authorization by the European Agency for the Evaluation of Medicinal Products (EMA) between January 1995 and September 2001, 47 (33%) were available for use in children and 10 had paediatric dosage forms [11]. Similarly, of the 45 new substances licensed by the EMA between January 1995 and April 1998, 29 were considered to be of potential use in children but only 10 (22%) were licensed for use in children [19]. In Australia there has been even greater discrepancy between the licensing of new chemical entities for children and for adults, where between 1998 and 2002 only 13% of new chemical entities were licensed for paediatric use [18]. Also in Australia, of those medicines licensed for paediatric use, around 25% did not have a paediatric dosage form [20].

In the USA the Food and Drug Administration Modernization Act (1997) and the Best Pharmaceuticals for Children Act (2002) have been implemented in order to encourage the development and marketing of medicines and suitable formulations for paediatric use [21, 22]. Under these programmes the market exclusivity of a chemical entity can be extended by 6 months if agreed clinical trials are undertaken for the paediatric age group. These incentives appear to have resulted in improved access to medicines for the older age groups of children, but it remains to be seen whether access for

neonates and infants will be improved [23]. In the UK, proposed incentives for licensing of medicines for children (such as extending market exclusivity) and the intention of developing a research infrastructure could lead to improvements in the availability of medicines for children [24, 25]. In addition, the European Union is in the process of developing legislation to encourage the licensing of medicines for children [26]. The present study could provide a baseline for monitoring the effects of these policies.

In the meantime, clinicians are left with the dilemma of whether to prescribe medicines for children when there is inadequate information available regarding efficacy, safety and, in some cases, stability. This situation may be partly remedied by Medicines for Children and the British National Formulary for children, which collate the available information regarding medicines for use in children, without being constrained by the product information [27, 28]. In addition, sharing of information between regulatory authorities could lead to more consistent labelling of medicines between countries. However, where such information is not available, should a medication be used in a child? Clinicians still need the freedom to be able to prescribe medicines, after duly considering the potential risks and benefits, in the best interests of the child.

A limitation to the present study was that although some of the newly introduced medicines in 2002 had acquired marketing authorization well before the year 1998, the SPC was neither included in the 1998 ABPI Compendium nor in the 2002 print version of the Medicines Compendium. The SPC of those products were identified in the 2002 Medicines Compendium CD-ROM version. This indicates that no information, possibly with the exception of package inserts, was available on those 'new medicines', although they were marketed in the UK in the years before 1998. As a consequence, health practitioners may have been unaware of alternative medicines or formulations that could be of potential use in children. The increased comprehensiveness of the CD-ROM version of the medicines compendium may also explain some of the overall increase in the number of medicines listed between 1998 and 2002.

The present study did not examine the influence of economics upon registration of medicines and could not determine whether the greater availability of medicines in the UK compared with Australia and New Zealand reflects market forces, rather than government policy towards the regulation of medicines for children. In addition, not all medicines may be of use in children, as indicated by only 64% of new chemical entities

approved for marketing by the EMEA between January 1995 and September 2001 being considered to be of potential use in children [11]. However, even entities that may initially appear to have no application in paediatrics may develop such indications over time [29].

The present study showed that there was an improvement in the availability of medicines for children in the UK over the 5-year period (1998–2002). There were no serious losses of useful medicines. The availability of medicines for children in the UK compares favourably with that for Australia or New Zealand.

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