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Effect of the Pediatric Exclusivity Provision on children's access to medicines

Joanne Grieve,[1] June Tordoff,[1] David Reith[2] & Pauline Norris[1]
[1]*School of Pharmacy, University of Otago, New Zealand,* [2]*Dunedin School of Medicine, University of Otago, New Zealand*

Correspondence
Dr David Reith, Section of Paediatrics and Child Health, Dunedin School of Medicine, 3rd Floor, Children's Pavilion, Dunedin Hospital, Great King St, Dunedin, New Zealand 9001.
Tel: + 64 34740999 Ext 8226
Fax: + 64 34747817
E-mail:
david.reith@stonebow.otago.ac.nz

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Aims
To determine the paediatric licensing status in the USA, UK, Australia and New Zealand of the 79 medicines granted paediatric exclusivity in the USA, and to assess the importance of those medicines to paediatric practice.

Methods
The medicines granted a patent extension in the USA as of 10 November 2003 were identified from the FDA website. Data on paediatric licensing were obtained from the Physicians Desk Reference (USA), the Electronic Medicines Compendium (UK), the Australian Prescription Products Guide (Australia) and the MedSafe website (New Zealand). A questionnaire was administered to seven paediatric consultants to assess the importance of the 79 PEMs for use in children. The questionnaire sought opinions on each drug, by age grouping, regarding: usefulness in patients with the condition, number of patients likely to be treated with each drug in a year, and acceptable therapeutic alternatives.

Results
Fifty-eight (73%) of the medicines had attained paediatric licensing in the USA. Sixty were licensed for adults in all four countries and of these 45 (75%) were licensed for children under 12 years in the USA compared with 31 (52%) to 33 (55%) for the other three countries. The proportion of these medicines licensed for children under 1 month, under 2 years and under 6 years of age ranged from 10% to 58% and there were no significant differences between the countries. For all four countries perceived usefulness and predicted numbers of patients both had some influence on the odds of a medicine having paediatric licensing.

Conclusions
Improvements in licensing of some medicines for children have occurred in the USA, relative to the UK, Australia and New Zealand, subsequent to the Paediatric Exclusivity Provision. Improvements occurred for children over the age of six, but not for younger children.

Introduction

Relatively few drugs that have undergone clinical trials and achieved licensing approval for adults have been approved for children [1]. As a result drugs needed for children are often used outside their licence recommendations. Since 1968, children have been described as 'therapeutic orphans', highlighting the paucity of medicines with paediatric licensing [2]. In the USA, the UK, Australia and New Zealand the majority of drugs licensed for adults have not been approved for children [3–6]. In 2002, 38% and 35% of drugs licensed for adults in Australia and New Zealand, respectively, were

licensed for children [5, 6]. Almost 80% of new substances licensed in Europe between 1995 and 1998 were not approved for children [7].

Of the agencies responsible for regulating the use of pharmaceuticals, the US FDA has been most active in encouraging paediatric drug licensing. In 1997, the Food and Drug Administration Modernization Act (FDAMA) was passed under Section 505 A of the Federal Food, Drug and Cosmetic Act. Under this scheme the FDA initiated Written Requests for clinical data [8]. If the pharmaceutical company submitted a satisfactory study report in response to the Written Request, the FDAMA offered a 6-month extension to patent exclusivity for all product lines of the chemical moiety (the Pediatric Exclusivity Provision). The FDA granted or denied the paediatric exclusivity based on the quality of the submitted report. While the FDAMA incentive programme ceased on 31 December 2001 a similar incentive programme emerged: the Best Pharmaceuticals for Children Act (BPCA), which was signed on 4 January 2002 [9]. This incentive programme is valid until 2007, and in addition to patent exclusivity incentives, establishes the Pediatric Pharmacology Advisory Committee and the Office of Pediatric Therapeutics in the FDA [10].

On 20 May 1998 the FDA, in consultation with experts in paediatric research, published a priority list of drugs (updated annually) which may be beneficial for children if supported by paediatric data [11]. Drugs on the list were defined as significantly improving therapeutic benefit compared with current drugs, providing a currently lacking therapeutic need, and being of wide potential use (at least 50 000 annual paediatric prescriptions in the USA) [12]. A drug need not be on the priority list for it to receive consideration for an exclusivity determination. As of November 2003, the FDA had issued 240 Written Requests to drug sponsors for paediatric studies [13]. At November 2003, 92 paediatric exclusivity determinations had been made, and 79 chemical moieties granted paediatric exclusivity [13].

In Australia recommendations to improve licensing of medicines for children include: implementing guidelines for the registration of drugs in children, encouraging the inclusion of children in clinical trials and requesting the submission of data in support of updating the product information to include information on paediatric use. In addition, the Australian Therapeutic Goods Administration is prepared to waive evaluation fees for orphan drugs (a drug for which the patient population is likely to be smaller than 2000). In the UK paediatricians and pharmacists took on the task of improving the safety of medicines for children by producing the 'Medicines for Children' formulary in 1999 [14]. This formulary gives prescribing information on licensed, unlicensed and off-label drug use. In addition, there are proposals by the European Commission to offer similar patent extensions to the USA in exchange for paediatric data. In New Zealand the Medicine and Medical Device Safety Authority (MedSafe) provides no incentive to encourage drug companies to conduct paediatric studies or seek paediatric licensing.

Whilst the US paediatric exclusivity provisions are an attempt to increase access to licensed paediatric medicines for children in the USA, some questions remain. It has not been demonstrated that the US paediatric exclusivity provisions have widened children's access to licensed medicines in the USA compared with other countries, or whether similar legislation in other countries would improve children's access to licensed medicines. The programme may not lead to increased access for all paediatric age groups, but may just improve access for those easier to study such as the over 6 years age groups. It is also not clear whether the medicines granted paediatric exclusivity provide significant health benefits for children.

This study aims to determine the paediatric licensing status in the USA compared with three similar countries (UK, Australia and New Zealand) of the 79 medicines granted paediatric exclusivity in the USA, and to assess the importance of those medicines in paediatric practice.

Methods

The medicines which had been granted a patent extension (PEM) in the USA as of 10 November 2003 were identified from the FDA website [13]. Data on paediatric licensing in the USA was obtained from the Physicians' Desk Reference or from pharmaceutical company websites [15–20]. The data included: generic name, trade name, therapeutic indication, type of formulation, and paediatric licensing information. Data for UK medicines was obtained from the Summaries of Product Characteristics (SPC) found in the Electronic Medicines Compendium [21]. For Australia the same data were obtained from the Product Information sheets in the Australian Prescription Products Guide (APP Guide) and for New Zealand from data sheets on the MedSafe website [22, 23]. Paediatric age categories were defined according to ICH guidelines [24]: term newborn infants (0–27 days); infants and toddlers (28 days to 23 months); children (2–11 years); and adolescents (12–16/18 years). The PEMs were divided into anatomical therapeutic chemical (ATC) groups using the searchable ATC classification index of the World Health Organization's Collaborating Centre for Drug Statistics Methodology [25]. Comparisons were made between the paediatric

licensing status of those medicines licensed for any age group in all four countries using the χ^2 test.

A questionnaire was administered to a selected panel of seven paediatric consultants in New Zealand and Australia to assess the importance of the 79 PEMs for use in children. The panel was asked to: (a) rate, for each age grouping the usefulness in patients with the condition (ranked on a scale of 1–5, where 1 represented 'not at all useful' and 5 represented 'essential') (b) estimate the number of patients, for each age group, likely to be treated with each drug in a year (c) nominate the existence of an acceptable therapeutic alternative, and (d) name the alternative. Information on the paediatricians' qualifications, years in practice and clinical interests was also sought. Logistic regression was undertaken to determine the influence of (a) perceived usefulness and (b) number of patients likely to be treated each year, on licensing for children for each age group using STATA 8.0 [26]. The suggested therapeutic alternatives for the PEMs were examined for paediatric licensing status. Alternatives that also appeared in the PEM list were excluded.

Results

A total of 79 chemical entities were identified which had been granted a patent extension through the FDA's Paediatric Exclusivity Provision as at November 2003. All of the PEMs were licensed for adult and/or paediatric use in the USA. The paediatric licensing status in the USA, UK, Australia and New Zealand of the PEMs is summarized in Table 1, along with information on ATC classification. Although a higher proportion of these medicines was licensed for use under 18 years age in the USA than in the other countries, only 58 (73%) of the medicines had attained paediatric licensing status in the USA. There were no differences between the UK, Australia and New Zealand in the proportion licensed for paediatric use. Relatively fewer medicines in the cardiovascular, antineoplastic/immunomodulating and musculoskeletal ATC groups were licensed for paediatric use. Conversely, relatively more medicines in the dermatological, respiratory and anti-infective groups were licensed for paediatric use.

The licensing of the 79 chemical entities for both adults and children varied between the countries and only 60 were licensed in all four countries (Table 2). When these 60 medicines were compared, a greater proportion was licensed for children under 12 years in the USA than the other three countries (Table 3). However when compared within age group, there were no significant differences between the countries in the proportion of the medicines with licensing for children under 6 years, under 2 years and under 1 month of age. Although it was not statistically significant, for the under 1 month age group a greater number of these medicines were licensed in the UK and New Zealand than in the USA.

For all four countries, perceived usefulness and predicted numbers of patients both had some influence on the odds of a medicine being licensed for paediatric use (Table 4). The relationship of paediatric licensing with perceived usefulness was more apparent in the USA and

Table 1
Licensing status of the drugs granted paediatric exclusivity

ATC description	Drugs granted paediatric exclusivity (p)	Licensed for paediatric use, *n* (% of p) USA	UK	Australia	New Zealand
Alimentary tract and metabolism	8	6 (75)	3 (38)	3 (38)	4 (50)
Cardiovascular system	16	8 (50)	2 (12)	0 (0)	1 (6)
Dermatologicals	4	4 (100)	2 (50)	2 (50)	3 (75)
Genito-urinary system and sex hormones	1	1 (100)	1 (100)	1 (100)	1 (100)
Antiinfectives for systemic use	8	8 (100)	6 (75)	6 (75)	6 (75)
Antineoplastic and immunomodulating agents	6	2 (33)	2 (33)	1 (17)	2 (33)
Musculoskeletal system	5	3 (60)	1 (20)	1 (20)	1 (20)
Nervous system	16	11 (69)	9 (56)	9 (56)	8 (50)
Antiparasitic products, insecticides and repellents	1	1 (100)	1 (100)	1 (100)	1 (100)
Respiratory system	9	9 (100)	9 (100)	8 (89)	8 (89)
Sensory organs	5	5 (100)	2 (40)	2 (40)	1 (20)
Total	79	58 (73)	38 (48)	34 (43)	36 (46)

Table 2
Number and percentage of paediatric exclusivity medicines (PEMs) licensed for children in four countries

Country	Number of PEMs Marketed for any age group (m)	Number (%) of PEMs marketed and licensed for children, n (% of m)				
		Any paediatric age group	0–27 days	28 days–23 months	2–11years	12–16/18 years
USA	79	58 (73.4)	4 (5.1)	8 (10.1)	32 (40.5)	58 (73.4)
UK	70	38 (54.3)	8 (11.4)	9 (12.9)	25 (35.7)	38 (54.3)
Australia	69	34 (49.3)	5 (7.24)	6 (8.7)	22 (31.9)	34 (49.3)
New Zealand	67	36 (53.7)	8 (11.9)	11 (16.4)	28 (41.8)	36 (53.7)

Table 3
Numbers of medicines licensed for children from list of 60 paediatric exclusivity medicines marketed in all four countries in common (chi-squared test)

Licensed for children younger than	New Zealand	Australia	UK	USA	*P*-value
12 years	33	30	31	45	0.02
6 years	30	25	28	35	0.32
2 years	22	19	19	22	0.88
1 month	9	6	8	6	0.79

UK, where there was a significant association for all the age groups. In Australia and New Zealand the relationship was significant for the older age groups. The association of number of patients with paediatric registration was weak, and was significant for the older age groups only. The panel suggested therapeutic alternatives for 47 of the 79 PEMs. Thirty-two were licensed for children under 18 years in New Zealand, 30 for children under 12 years and 24 for children under 6 years.

Discussion

The present study indicates that the USA has been more successful at achieving paediatric licensing for selected medicines, but only for the older age groups. For the younger age groups there were no differences between the USA, and three similar countries with no incentives for paediatric licensing. This may be because clinical trials are easier to recruit and conduct in children over the age of 6 years. In addition, if paediatric exclusivity can be obtained with data from children in the 6–12 years age group then there is no incentive to study the medicines in the younger age group unless market forces dictate a commercial advantage. The association of licensing with perceived usefulness and patient numbers also indicate that even within those drugs granted paediatric exclusivity, the utilization of the drug influences the likelihood of paediatric licensing.

In Australia and New Zealand few of the recently marketed drugs have been licensed for paediatric use [5, 6]. In Australia, of the 90 new orally available chemical entities licensed for adults between 1998 and 2002 only 12 (13%) were licensed for children [6]. In New Zealand improvements in paediatric licensing, where present, appear to primarily benefit the older age groups of children [5]. In Europe, only 10 of 45 new substances licensed between January 1995 and April 1998 were licensed for paediatric use [7]. Hence, there is considerable interest in whether the incentives used in the US regulatory system will deliver increased paediatric licensing of medicines, such that the European Commission is considering introducing similar legislation.

Since June 1998 the FDA has issued Written Requests for paediatric studies to sponsors of 240 chemical entities [13]. There is no requirement for sponsors to undertake studies but if a study application is approved, the drug is eligible for a 6-month patent extension. The 240 drugs were selected in consultation with paediatric research experts, according to their likelihood of providing an increased health benefit to children, and issued to sponsors by the review divisions of the Center for Drug Evaluation and Research (CDER) [13]. As at November 2003 the FDA had made 92 Pediatric Exclusivity Determinations from the original list of 240 drugs. Of these 92 drugs, 79 were granted paediatric exclusivity' or patent extensions [27]. The remaining 161 drugs not given a Pediatric Exclusivity Determination consist of a mixture of pending studies, rescinded Written Requests and declined Written Requests.

From the 79 drugs granted paediatric exclusivity, we identified only 58 (73%) that are licensed for paediatric

Table 4
Influence of usefulness, and the estimated number of patients that could be treated with the drug, upon licensing expressed as OR (95% CI)

	Usefulness	Number of patients
USA: 0–27 days	1.55 (1.07–2.25)	1.07 (0.73–1.56)
USA: 1–23 months	1.89 (1.42–2.52)	1.02 (0.94–1.11)
USA: 2–5 years	1.95 (1.57–2.44)	1.05 (1.01–1.08)
USA: 6–11 years	1.72 (1.35–2.19)	1.02 (1.00–1.05)
UK: 0–27 days	1.58 (1.25–1.99)	1.37 (1.10–1.69)
UK: 1–23 months	1.66 (1.29–2.14)	1.06 (0.99–1.14)
UK: 2–5 years	1.65 (1.32–2.07)	1.09 (1.04–1.14)
UK: 6–11 years	1.52 (1.19–1.96)	1.06 (1.02–1.10)
Australia: 0–27 days	1.15 (0.83–1.59)	*
Australia: 1–23 months	1.30 (0.96–1.77)	1.04 (0.96–1.12)
Australia: 2–5 years	1.74 (1.37–2.21)	1.11 (1.05–1.17)
Australia: 6–11 years	1.64 (1.26–2.13)	1.06 (1.02–1.09)
New Zealand: 0–27 days	1.26 (0.98–1.60)	0.88 (0.59–1.30)
New Zealand: 1–23 months	1.45 (1.16–1.81)	1.05 (0.98–1.12)
New Zealand: 2–5 years	1.71 (1.37–2.13)	1.21 (1.10–1.33)
New Zealand: 6–11 years	1.87 (1.44–2.43)	1.14 (1.07–1.21)

**No patients anticipated for the registered drugs.*

use in the USA. This apparent anomaly is accounted for by the FDA's explanation that granting of paediatric exclusivity is independent of giving approval for paediatric use. After the FDA issues a Written Request, the drug sponsor may voluntarily submit paediatric studies as part of their application for paediatric exclusivity, or be granted a deferral or waiver. The FDA must then determine whether the sponsor has satisfied the terms of the Written Request within 90 days. This would usually occur before the review of the sponsor's submission is completed, causing paediatric exclusivity to be granted before the drug is actually approved (or not) for paediatric use. Drug label changes may be made once the FDA has completed its review and a decision has been made whether to approve the drug for paediatric use.

Not all of the paediatric exclusivity rulings resulted in paediatric labelling. In the case of some of the medicines this may be related to a lack of effectiveness, and/or an apparent increase in adverse effects in the paediatric or adolescent age groups [28]. There were also cases in which the original licence was relabelled with further age restrictions to protect children from adverse effects discovered during paediatric trials. For example after paediatric studies, the licensing age for the dermatitis medicine pimecrolimus (Elidel® cream) was raised from 3 months to 2 years [27]. These cases should be counted as successes for the paediatric exclusivity rule due to the provision of useful data that may not have otherwise been obtained. For some of the other medicines granted paediatric exclusivity, but not yet licensed for paediatric age groups, a delay in the process of evaluation may explain the discrepancy.

For the limited number of drugs included in the present study it appears that perceived drug usefulness is one of the driving forces for drug registration, while the weaker influence of patient numbers suggests that market size does not drive drug licensing for children. This may be caused by at least two factors: drug companies may be altruistic in performing paediatric studies for drugs useful to children, or companies may consider that the users will be willing to pay more for drugs with greater perceived usefulness. Another factor that may influence paediatric licensing is whether the 79 drugs surveyed are in fact useful or necessary drugs. If there are suitable therapeutic alternatives which are licensed for children, there is no real necessity to license more drugs for the same therapeutic indication. However the present study indicated that only 47 (59%) had therapeutic alternatives and only 32 (41%) were licensed for children under 18 in New Zealand. These findings support a need for greater drug licensing for children.

The limitations of the present study include the small panel of paediatricians, and their restriction to Australasia; the rare nature of some of the conditions that would be treated with some of the drugs, and the lack of access to information about some FDA decisions. This study's generalisability is limited by its small invited panel of seven paediatricians mostly from New Zealand and one from Australia. A future study would be strengthened by a larger panel with experts drawn from all of the coun-

tries in which drug licensing was surveyed. A further limitation is the extent of the general paediatricians' experience with the wide, new and novel range of drugs presented in the list of 79 PEMs. General paediatricians do not use many of these drugs in their daily practice, and hence are limited in their ability to evaluate the usefulness of those drugs. In future studies this could be overcome by surveying a range of expert paediatricians to rate usefulness and frequency of use of their particular drugs, for example: paediatric infectious disease physicians, paediatric nephrologists, metabolic physicians, and child psychiatrists.

In conclusion, improvements in licensing of some medicines for children have occurred in the USA, relative to the UK, Australia and New Zealand, subsequent to the Pediatric Exclusivity Provision. These improvements are measurable for children over the age of six, but not for younger children. Paediatric licensing is influenced by the perceived usefulness of medicines for children.

Competing interests: None declared

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