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Unlicensed and Off-label Drug Use in Australia

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Abstract

Off-label and unlicensed drug use is an area of concern in Australia and resulted in the recent publication of two key documents: the Australian Drug Evaluation Committee's (ADEC) Report of the Working Party on the Registration of Drugs for Use in Children *and the Australian Association of Paediatric Teaching Centres' (AAPTC) policy document* Pharmaceuticals for Children. *These highlight many of the problems that the current licensing system produces, such as the lack of paediatric licensing, inadequate paediatric information, lack of suitable formulations and the financial inequity that the use of unlicensed and off-label drug usage invokes. These documents have been supported by a limited number of published Australian studies that have quantified the extent of the problem. The impetus to change the current system, generated by this body of work, needs to be maintained and it is essential that the Therapeutic Goods Administration, the pharmaceutical companies and the professions act upon the recommendations outlined.*

Key words: Licensing – Off-label – Children

Introduction

Over recent years the use of unlicensed and off-label drugs in Australian children has been an area of concern, as it has in other countries. This culminated in the publication of two key documents in 1997: the Australian Drug Evaluation Committee's (ADEC) *Report of the Working Party on the Registration of Drugs for use in Children*[1] and the Australian Association of Paediatric Teaching Centres' (AAPTC) policy document *Pharmaceuticals for Children*[2]. These documents highlight many of the issues of inequity of access to medicines that Australian children endure. These include problems common to paediatric practitioners world wide, such as:

- Inadequate information on which to base doses in paediatric patients.
- Lack of suitable formulations.

They also highlight problems more specific to the Australian registration process, such as the financial disadvantage for families and children in the way in which medicines are provided.

A number of recommendations required to improve the current situation are made. These include:

- Rationalisation of current procedures to facilitate registration of drugs for use in children.
- Immediate registration of most drugs for children from 12 years of age.
- Removal of disincentives to registering drugs for use in children.
- Resourcing of the Therapeutic Goods Administration (TGA) to enable appropriate action.
- The introduction of simplified and inexpensive registration arrangements to encourage the pharmaceutical industry to market paediatric formulations which are registered and supplied in foreign countries.

The Medicine Registration Process in Australia

Medicines undergo a similar registration process in Australia to the UK. Pharmaceutical manufacturers make a submission to the Therapeutic Goods Agency (TGA) (this is equivalent to the

Medicines Control Agency in the UK) for approval to market a drug. This submission includes data on the manufacturing process and all preclinical and clinical studies. If the TGA recommends registration, this data is then submitted to the Australian Drug Evaluation Committee (ADEC) for approval. Drugs can only be registered for purposes for which proven safety and efficacy data is provided. Once approved this allows a pharmaceutical company to market a medicine for specific indications and these appear in the approved product information. As in other countries, clinicians can use medicines outside the terms of the prescribing information (off-label), but the responsibility for ensuring the safety and efficacy of a particular treatment rests with the prescriber and/or their health-care institution.

The commercial realities of submitting a medication for registration in a relatively small marketplace such as Australia discourages pharmaceutical companies from the registration of some chemical entities and, in particular, formulations that the same company has marketed overseas (see Table 1).

There are a number of methods by which some of these difficulties may be overcome[3].

- Drugs may be 'imported for personal use'. In this case the drug must be for the use of the importer or a member of the immediate family, the quantity involved must be no more than three months' supply, and if the product could be obtained in Australia only with a medical practitioner's prescription, the importer must have the written authority of a registered medical practitioner.
- A pharmaceutical manufacturer may act as a sponsor of a medication that is approved overseas but not in Australia. In this situation the pharmaceutical manufacturer will undertake the importation of the medicine and will supply it on request providing approval has been granted by ADEC. These medicines may be awaiting approval, e.g. clarithromycin suspension, or medicines that, for commercial reasons, the company does not intend to market in Australia, e.g. epoprostenol injection.

The scheme by which medicines are available in this manner is known as the Special Access Scheme (SAS).

- If a drug company is unwilling to sponsor a drug then direct importation from overseas by the hospital pharmacy or by the prescriber is possible, e.g. via an overseas wholesaler or pharmaceutical manufacturer.

Prescribers require approval under the SAS for these patients only.

In both of the above circumstances a record of who received the medicine, the dose, indication, etc must be kept. This is similar to the 'named patient' scheme in the UK.

However, it should be noted that the availability of a medicine overseas does not guarantee that importation will be allowed. ADEC will only grant approval for drugs that ***it*** considers for 'the treatment of life-threatening conditions for which there is no alternative product available'.

Table 1. Examples of medicines and formulations available overseas but unavailable in Australia

Drug	Comments
Trimethoprim suspension	Trimethoprim suspension is unavailable commercially as a single agent and therefore co-trimoxazole suspension is routinely used
Oxybutynin suspension	Not marketed in Australia – manufactured by a TGA-licensed manufacturing unit
Acyclovir suspension	Not marketed in Australia – dispersible tablets used
Diclofenac paediatric suppositories	Diclofenac 100 mg suppositories are approved but not the 12.5 mg, 25 mg and 50 mg paediatric sizes
Augmentin* (amoxycillin and clavulanic acid) injection	Augmentin injection is unavailable although the Augmentin* tablets and suspension are
Epoprostenol injection	Not marketed in Australia – available through the Special Access Scheme
Diazepam rectal solution	Not marketed in Australia – manufactured by a TGA-licensed manufacturing unit
Baclofen liquid	Not marketed in Australia – manufactured by a TGA-licensed manufacturing unit
Carbamazepine suppositories	Unavailable in Australia
Sodium valproate injection	Unavailable in Australia

- There are a number of TGA-licensed manufacturing units. These prepare a range of pharmaceutical products, often paediatric formulations of medicines, and are similar to the 'specials' manufacturers in the UK. The TGA licence guarantee's the quality of the product but responsibility for the prescribing, choice of dosage and safety of a medicine rests with the prescriber.
- Participation in a clinical trial.
- In 1998 an Orphans Drug Program was established in Australia with the aim of developing drug products intended to treat rare diseases and to encourage marketing through financial incentives. A drug product is designated as an orphan drug in Australia if its use is intended in 2000 or fewer individuals. This program is in its early stages but it is hoped that it will lead to improved access to a range of specialist medicines. However, this will only be of benefit to a small number of patients who fulfil the above criteria.

The availability of medicines via these methods does not overcome many of the fundamental issues of off-label and unlicensed use, such as the lack of prescribing information and safety data. The use of these medicines also leads to difficulties with ensuring continuation of supply. This is of particular concern given the vast geographical distances and remoteness of many patients in Australia.

Financial Inequity

Unlike the UK, where children under 16 years of age are exempt from a prescription charge, there is a financial cost for medicines supplied to children in Australia. The current system financially disadvantages Australian children if they are prescribed unregistered or off-label medications.

Once a drug has received registration approval it may be submitted to the Pharmaceutical Benefit's Advisory Scheme which recommends whether it should be placed on the Pharmaceutical Benefit Scheme (PBS). If a drug is available on the PBS then it is available at a subsidised cost to the patient (currently from A$3.20 to A$20.60 (approximately £1.30 to £8.00 sterling) per item per calendar month). However, drugs are only available on the PBS if prescribed within certain restrictions, including the indication and length of treatment for which a drug can be prescribed. All unregistered medicines and medicines used off-label are unavailable on the PBS. When obtained outside the hospital environment, drugs not included on the PBS are charged at the cost price of the item plus the community pharmacist's fees. This is often far in excess of the A$20.00 subsidised cost. Also, many of the items prescribed within hospitals are hospital products only and would be unavailable outside.

Studies in Australia

Only three published Australian studies have investigated issues surrounding the use of unlicensed and off-label use in paediatrics.

An audit of the 1994 Australian MIMS showed that 72% of the prescription drugs listed either provided no information at all about paediatric use or contained a partial or general disclaimer about use in children[1]. This figure is comparable with the 81% obtained by the same analysis of the 1991 US Physicians Desk Reference[4].

South Australian researchers showed that 50% of medicines prescribed for paediatric hospital ambulatory patients were not listed on the PBS benefits[5] and hence would have been financially disadvantaged by the current system.

The most recently published study reported the extent of off-label and unregistered drug use in Australian children[6]. 15.3% and 17.1% of drugs administered on a surgical and medical ward, respectively, were used off-label or were unregistered[6]. 36% of patients received unregistered or off-label drugs. Using the same methodology, a similar study in the UK[7] found that 25.2% and 25.1% of drugs administered on a surgical and medical ward, respectively, were used for off-label use or were unregistered, and that 36% of patients received unregistered or off-label drugs. This study shows that the extent of unlicensed and off-label use in Australian children is similar to the UK.

These studies give an indication of the significance of this problem in Australia and in future should allow quantitative analysis of whether improvements in the registration process for children have been made.

Summary

The recently published initiatives by the AAPTC and ADEC are welcomed. The strategies suggested to improve this situation are similar to those put forward in the UK and in the USA. These include changing the current registration process for pharmaceuticals, empowering ADEC to require paediatric data as part of the registration application and ensuring that paediatric data is included in the prescribing information of those pharmaceuticals which have an actual or potential use in childhood disease. However, it should be remembered that the Food and Drug Administration (FDA) issued regulations in 1994 to

encourage drug manufacturers to submit paediatric data voluntarily for review, and while these voluntary efforts were helpful, they made little real impact. In November 1998 new FDA regulations were introduced that required all new drugs that are therapeutically important for children, or will be commonly used in children, to have paediatric labelling information.

It is important that the current impetus to improve the situation in Australia is maintained and there is a need to ensure that the TGA, the pharmaceutical companies and the professions act upon the proposals suggested.

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