

'Off Label' Drug Use in Children

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Introduction

Three quarters of all medications marketed today do not carry Food and Drug Administration (FDA) approved labeling for use in neonates, infants, children and adolescents. This has been stated by the pediatric pharmacology research unit Network which is established by the national institute of Child Health and Human Development in the United States. It is shocking to note that few drugs, only approximately 20% of all drugs marketed in the United States, have been labeled for use by infants and children. Eighty percent or more of drugs approved since 1962 have been approved and labeled for use in adults with a disclaimer in the labeling that they are not approved for use by children (as indicated by the American Academy of Pediatrics in September 12,1996). Many commercially available drugs are only licensed for use in adults and are not used according to the product licensing in pediatric practice.

Only minorities of the currently marketed drugs have undergone pediatric clinical trials and have approved labeling for use in children. These include common antimicrobial agents, medications for fever, vaccines and some asthma and allergy medications. However, most drugs used to treat illnesses in children have never been formally tested or approved for pediatric use and lack even basic dosage recommendations for children in their labeling. These include such routinely used medications as dopamine (used to treat shock), cisapride (used to treat abnormal regurgitation of stomach contents in infants and small children), ketorolac (the only available injectable non-narcotic pain reliever), midazolam (used as a sedative and to treat convulsions) and adenosine (used to treat life threatening abnormal heart beats) and the list is much longer.

The treatment of pediatric patients with drugs in hospitals is being impeded by a shortage in the availability of licensed drugs in an appropriate formulation. There are several reasons for this situation, ethical problem of research in children, the reluctance of parents to allow their children to participate in drug trials and the technical challenges small study participants bring along. Possibly because of the underestimation of the problem, there is a lack of funding from governments, health care providers and industry. As a result, pediatric drug trials are relatively scarce and in many cases contain only a limited number of patients. The purpose of licensing is to ensure that medicines are examined for safety, efficacy and quality. Most medicines administered to adults have a product license that outlines the particular indication, dose and route of administration for a drug. However, many medicines used for children are not licensed for use in children or are used outside the terms of product license ('off label'). This means that the risks or benefits of using a drug in that particular situation have not been examined by the licensing authority.

The aim of this review is to emphasize the need to make studies and to focus on dosing and safety data for children in an appropriate pediatric population a requirement during clinical trials of each new drug with potential use by children.

This review also discusses the operation of the licensing system and the use of unlicensed and off-label drugs in children.

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The Licensing System and the Role of the Medicines Control Agency (MCA):

The Medicines Act 1968 requires that all medicines manufactured or marketed must have been licensed by the Licensing Authority, which the Health Minister is acting through the MCA, an executive agency of the Department of Health. As previously stated, the licensing system is designed to ensure that medicines are examined for efficacy, safety and quality. Pharmaceutical companies apply for Product License (PL) for a particular drug and their submission includes the indication, dose, route of administration and age group of patients for whom this particular drug is applied. When first submitted for licensing, the amount of information on pediatric use may be limited or absent, leading to statements in the data sheet such as contraindicated in children or insufficient information to recommend use in children.¹⁻⁸

Recent European legislation allows a license application in one EU country to apply to all of the member states and replaces product licenses with 'Marketing Authorization' (MA) and the data sheet with a 'summary of product characteristics'.

Licensing arrangements constrain pharmaceutical companies but not prescribers. The Medicines Act 1968 and European legislation makes provision for doctors to use medicines that do not have a PL or MA (Unlicensed) and for purposes other than stated in the PL or MA.

Off-Label Drug Use

'Off-Label' is an Americanization (or short hand term) describing the use of licensed medicines outside the terms of their PL or MA.^{1, 4, 6} Use of a medicine may be 'off-label' for one of several reasons:-

1. Dose: Medicines may be given at doses other than those stated in the PL or MA.

Example: ipratropium bromide nebulizer are licensed to be given up to three times daily but in hospital practice are used more frequently than this.

2. Indication: Medicines may be used for indication other than those stated in the PL or MA.²

Example: Epoprostenol is licensed as an alternative to heparin during dialysis. It is used as a vasodilator in primary pulmonary hypertension of the newborn and for its antiplatelet action in the treatment of disseminated intravascular coagulopathy.

3. Age: Medicines may be used outside their licensed age range. Some medicines are 'not recommended in children.'⁸

Example: The PL for omeprazole states 'there is no experience of the use of omeprazole in children' although it is frequently used in this age group. Other medicines are licensed for use in children but only at a specific age range. Example: salbutamol syrup is not licensed for children less than two years of age, yet it is frequently used in this age group.

4. Route: Many medicines are given by unlicensed route.

Example: vitamin K injection is often administered orally to newborns to prevent hemorrhagic disease because there is no suitable licensed preparation.

5. Contraindications: Many medicines are contraindicated for use in children.

Example: Aspirin is not recommended for use in children because of its association with Reyes syndrome. However, aspirin is used for its antiplatelet action in the treatment of Kawasaki disease and in some cardiac patients.

Other examples of off-label medicines used in infants and children are shown in table (1).

Unlicensed Drug Use

The use of medicines without a PL or ML can be classified as follows:-

1. Modifications to a Licensed Medicine.

The PL specifies the form, appearance and packaging of a medicine and any changes to these characteristics render the medicine unlicensed.

This includes extemporaneous dispensing, the common practice of taking an 'adult' dose and turning it into a preparation suitable for a child such as an oral liquid.⁸

Examples: Preparation of ciprofloxacin suspension from tablets.

2. Medicines that are licensed but the particular formulation is manufactured under a 'special' manufacturing license.

This may be because the adult preparation is not suitable for use in children and there is a need for a smaller dosage form.⁸

Example: Digoxin pediatric injection (100 microgrammes per ml).

In other cases, there may be no suitable licensed dosage form.

Example: Flecainide suspension.

3. Medicines that are not licensed but are produced under a 'special' manufacturing license.

These may be novel medicines that are not commercially viable for a manufacturer to take through the licensing process (the so-called 'orphan drugs').¹

Examples: Caffeine injection for apnea of prematurity and sodium phenylbutyrate injection for the treatment of hyperammonaemia. The 'special' manufacturing license is granted to suitable National Health Service (NHS) or commercial manufacturers and is concerned with the quality assurance of the manufacturing process. It does not include the assessment of safety, quality or efficacy of the manufactured medicine provided by the PL or MA application.

4. Use of Chemicals as Medicines.

In some pediatric diseases, particularly rare metabolic disorders, there may be a need to use chemicals as medicines because there are no licensed medicines available and no pharmaceutical material of recognized standard.

5. Medicines Used Prior to the Granting of a License.

These may be medicines for which a PL is awaited (named 'patent' medicines).

Further examples of unlicensed drug use are given in table (2).

Table 1: Examples of off-label drug use.

Off-Label	Examples
Indication	<i>Dinoprostone is licensed as an oxytocic agent but is used in pediatric cardiac patients to maintain a patent ductus arteriosus. Immunoglobulin (Sandoglobulin®) is licensed for the treatment of idiopathic thrombocytopenic purpura and hypogammaglobulinemia but is also used in the treatment of Kawasaki disease and epilepsy.</i>
Dose	<i>Dalivit® multivitamin drops are licensed for infants less than one year in a dose of 0.3 ml daily. In cystic fibrosis patients, 1ml daily is given. Salbutamol (Ventolin®) nebulES are licensed in adults for doses of up to 40mg daily. In practice, older children may receive up to 60 mg daily.</i>
Age	<i>Diazepam (Stesolid®) rectal solution is not licensed for children less than one year. Fluticasone (Flixotide®) inhalers are not recommended under the age of four years. Amiloride (Midamor®) tablets are not recommended for use in children. All these drugs are used outside the licensed age range.</i>
Route	<i>Adrenaline injection is nebulised to treat group. Potassium Chloride 15% injection is given orally as a potassium supplement. Lorazepam (Ativan®) injection is used rectally to treat status epilepticus.</i>
Contraindication	<i>Ciprofloxacin (Ciproxin®) is not recommended in children because it has been linked to arthropathy in weight bearing joints of immature animals. Tetracycline is not recommended in children because it is selectively taken up in developing bones and teeth and may lead to dental staining and hypoplasia.</i>

Table 2: Examples of Unlicensed Drug Use. ⁸

<i>Reasons of Unlicensing Drug</i>	<i>Examples</i>
<i>Modification to licensed medicine. e.g.: extemporaneous preparation by a central Intravenous Additive.</i>	<i>Amiodarone suspension Cyclosporin eye drops</i>
<i>Medicines which are licensed but the particular formulation is manufactured under a 'Special' license</i>	<i>Frusemide 10mg/ml suspension Hydralazine 12.5 mg tablets Propranolol solution 5mg/5ml</i>
<i>Chemicals used as medicines</i>	<i>Betaine powder Sodium phenylbutyrate Tobramycine powder</i>
<i>Novel medicines available as 'special' medicines</i>	<i>Caffeine injection Nitric oxide gas Tolazoline injection</i>
<i>Imported medicines</i>	<i>Chlorothiazid (Diuril®)</i>

Discussion

The product license for a drug is not actually published, but the product data sheet acts as a summary of the product license. Unfortunately, many data sheets are ambiguous in their statements for use in children. Making it difficult for health professionals to make informed decisions on the risk, benefits of using a medicine for a particular indication and often whether or not it is licensed in children, there is a need to improve the provision of pediatric information within the data sheets. Prescribing an unlicensed or 'off-label' medicine is not illegal, but it is a risk management that needs to be addressed.

In 1968, H. Shirkey an American pharmacologist, used the term 'therapeutic orphans' to describe the exclusion of infants and children from approved indications for most drugs approved by the Food and Drug Administration (FDA). ⁹ There has been no improvement over the last 30 years with approximately 80% of the drugs approved by the FDA having a disclaimer for use in children. ^{10, 11}

The reasons for a drug being unlicensed in children are many. It is often because the drug has not been tested in children. This may be due to financial constraints or because of the apparent difficulties with trial design and ethics testing drugs in children. This is unacceptable, as children deserve the same safeguards as adults.

There has only been one published study that has looked at the extent of unlicensed 'off label' drug use in the UK. ¹ This was undertaken on a pediatric intensive care unit and found that 35% of all drugs prescribed were unlicensed or used off label. 70% of all patients received one or more unlicensed or 'off-label' drugs. There is clearly a need for further research to quantify the extent of the problem in other areas, both in hospital and in the community.

In the US, unlicensed and off-label drug use has been recognized as an important issue and several initiatives have been investigated by the FDA and National Institute of Child Health and Human Development that promise to increase the number of drugs studied and labeled for children. ^{6, 12, 13} Similar schemes have been set up in Australia and Canada. ⁴

In the UK, a joint working party of the British Pediatric Association (now the Royal College of Pediatrics and Child Health) and the Association of the British Pharmaceutical Industry have produced a report on 'the licensing of medicines for children.' This report has made recommendations that the MCA should be seen to support and will encourage pharmaceutical companies to seek product licenses for the many medicines used in children.

Surveys in the United Kingdom by Turner et al, and by others, ^{1, 15- 20} have shown that many drugs prescribed to children in pediatric, and especially neonatal care are not licensed for children, or are prescribed 'off label' (i.e., outside the terms of the product license). In the United States, about 80% of all drugs approved for the market lack partial or complete information in the label pertaining to use in pediatric patients. ^{10, 21, 22}

The US food and drug administration has implemented new regulations to increase the number of drugs available for pediatric use.^{23, 24} In Europe, similar changes are under discussion, currently only with very limited success.^{25, 26}

Conclusion

Prescribing an unlicensed or 'off -lable' medicine is not illegal, but it is a risk management that needs to be addressed. So that the recognition of the importance of studying drugs for use in children and the establishment of various initiatives is to be applauded.

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References

1. Turner S, Gill A, Nunn T, Hewitt B, Choonara I. Use Of 'Off-Label' and Unlicensed drugs in pediatric Intensive Care Unit. *Lancet*. 1996; 347:549-550.
2. Prescribing unlicensed drugs or using drugs for unlicensed indications. *Drug There Bull*. 1992; 35:97-9.
3. Risk; Benefit analysis of drugs in practice. *Drug There Bull*. 1995; 33:33-5.
4. Gervais A. Comment: medications unlabelled for use in children. *Ann Pharmaeotherapv*. 1995; 29: 1052.
5. Committee on Drugs. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics*. 1995; 95: 286-94.
6. Kaufman RE. Status of drug approval processes and regulation of medications for children. *Curr Op pediatric*. 1995; 7: 195-8.
7. Nahata RE. Need for conducting research on medication unlabelled for use in pediatric patients. *Ann Pharmacotherapy*. 1994; 28:1103-4.
8. Zenk K. Chalanges in providing pharmaceutical care to pediatric patients. *Am J. Hosp Pharm*. 1994; 51:688-94.
9. Shirkey HC editorial comment. Therapeutic Orphans. *J Pediatric*. 1968; 72:119-120.
10. Gilman JT, Gal P. Pharmacokinetic and pharmacodynamic data collection in children and neonates. A quiet frontier [comment] *Clinical Pharmacokinet*. 1992; 23: 1- 9.
11. Wilson TJ. Pragmatic assessment of medicines available for young children and pregnant or breast-feeding woman. Morselli PL, Garattini S, Sereni F eds. *Basic and Therapeutic Aspects of Perinatal Pharmacology*. New York, NY. Raven Press. 1975:41: 1- 12.
12. Cote' CJ, Kaufmann RE, Troedle CJ, Lambert GHs the 'therapeutic orphan' about to be adopted? *Pediatrics*. 1996; 98:118- 23.
13. Committee on Drugs. Unapproved uses of approved drugs; the physicians; the package insert and the Food and Drug Administration; Subject Review. *Pediatric*. 1996; 98:143-5.
14. Licensing medicines for children. *British Pediatric Association*. London. 1996.
15. Nahata Mc. Licensing of medicines for children in the USA. *Pediatr perinat drug Ther*. 1997; 1:50-51.
16. Turner S, Nunn A, Choonara I. Unlicensed drugs use in children in the UK. *Paediatr Perinat Drug Ther*. 1997; 2:52-55.

17. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards. Propective study. *BMJ*. 1998; 316: 343-345.
18. Conroy S, McIntyre J, Choonara I. Unlicensed and off label drugs use in neonates *Arch Dis Child Fetal Neonatal Ed*. 1999; 80: F142-F144.
19. McIntyre J, Conroy S, Avery A, Corns H, Choonara I. Unlicensed and off label prescribing of drugs in general practice. *Arch Dis Child*. 2000; 83:498-501.
20. Chalumeau M, Treluyer JM, Salanave B, et al. Off label and unlicensed drug use among French office based pediatricians [in process citation]. *Arch Dis Child*. 2000; 83:502-505.
21. Guidance for Industry: Content and format for pediatric Use Supplements. Washington, DC: Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). 1996:1- 6.
22. Newman, C Hull D. Comment regulations for pediatric labeling of prescription drugs [letter; comment] *Ann Pharmacother*. 1997; 31: 1092-1093.
23. Department of Health and Human Services. Food and Drug administration. 21 CFR Parts 201, 312,314 and 601: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of new Drugs and Biological Products in Pediatric Patients. Rockville, MD: Food and Drug Administration, Center for Drug Evaluation and Research. 1998: 66632-66672.
24. Federal Register 21 CFR Part 201. Requirements on content and format of labeling for human prescription drugs and biologics. Requirements of prescription drug product labels; proposed rule. 2000.
25. Kmietowicz Z. Drug industry is unwilling to run trials in children. *BMJ*. 2000; 320: 1362A.
26. Impicciatore P, Choonara I. Status of new medicines approved by the European medicines evaluation Agency regarding pediatric use. *Br J Clin Pharmacol*. 1999; 8: 15- 8.

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عمان

ملخص:

هذا ما تم إثباته من قبل وحدة أبحاث الأطفال والصيدلة والتي أسست من قبل المعهد الوطني لصحة الطفل وتطور الإنسان في الولايات المتحدة الأمريكية. إنها لمفاجئة أن نلاحظ أن عدد قليل من الأدوية، فقط حوالي 20% من جميع الأدوية التي تباع في الولايات المتحدة عليها علامة الاستعمال في الرضع والأطفال.

خمسة وسبعون بالمئة من جميع الأدوية التي تباع في الأسواق لا تحمل علامة موافقة إدارة الغذاء والدواء في الولايات المتحدة الأمريكية لاستعمالها في حديثي الولادة والرضع والأطفال البالغين.