COMMITTEE ON CHILDREN AND YOUNG PEOPLE

INQUIRY INTO THE USE OF PRESCRIPTION DRUGS AND OVER-THE-COUNTER MEDICATIONS IN CHILDREN AND YOUNG PEOPLE

ISSUES PAPER No. 4

THE USE BY CHILDREN AND YOUNG PEOPLE OF PRESCRIPTION DRUGS AND OVER-THE-COUNTER MEDICATIONS DEVELOPED FOR ADULTS

Submissions and Further Information

The Committee on Children and Young People invites written comment from interested organisations, groups and individuals regarding any of the matters raised in this Issues Paper. Ideally, comments should be forwarded to the Committee on Children and Young People, Parliament House, Macquarie Street, SYDNEY NSW 2000 by Monday 29 July 2002, although the Committee will continue to accept and consider comments after that date. Submissions may also be forwarded by fax on (02) 9230 2928, or email: children@parliament.nsw.gov.au. Further information on the Inquiry or on how to make a submission can be obtained from Mr Ian Faulks, Manager of the Committee, on (02) 9230 2161. Further information about the Committee on Children and Young People can be viewed on the Committee's web site at: www.parliament.nsw.gov.au/gi/commits/children.

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INTRODUCTION

This Issues Paper explores the use by children and young people of prescription drugs and medication developed for adults.

Several submissions from individuals and organisations expressed concern about various aspects of this issue.[1] Some concerns relate to other areas of this inquiry, for example, the use of psychotropic drugs developed for adults in children with challenging behaviour, including those in state care.[2]

Issues examined in this paper

- The regulation and licensing of prescription drugs and medication for paediatric use
- Encouraging registration and licensing of drugs for paediatric use
- The off-label prescription of drugs for paediatric use:
  (a) Extent of off-label prescription
  (b) Medico-legal issues
  (c) Off-label prescription and the PBS
  (d) Possible risks of off-label prescription of drugs for use by children and young people
- Reasons for a lack of paediatric testing
- Improving research into drugs for paediatric use

Please see **Issues Paper No. 1** for information about the Inquiry, the Committee for Children and Young People and how to make further submissions. **Issues Paper No. 1** also contains background and contextual information about the subject matter of the Inquiry .

REGULATION AND LICENSING

The regulation of prescription drugs and medication for use by children and young people, is based on the recognition that there is a need for specific paediatric labelling of products.

There is no easy extrapolation from adult studies to children, as children's physiological systems are different from adults and the results of medication (including toxicity) can be very different.

Children are not young adults

If no paediatric trials are conducted warnings are required

Commonwealth legislation requires that if no specific paediatric trials have been conducted on a product, certain warnings must be displayed on the label.

The pharmaceutical company must include in the product information comments such as: 'safety and effectiveness has not been established in children'; 'unapproved for use in children under twelve years of age'; and 'not recommended for children under the age of twelve', depending on the product.

ENCOURAGING REGISTRATION OF DRUGS FOR PAEDIATRIC USE

ADEC Report

In 1997, the Australian Drug Evaluation Committee (**'ADEC'**), recommended that paediatric data should be submitted as part of an application for registration for *all* drugs, where there might be a relevant paediatric indication.[3]

The Australian Drug Evaluation Committee also recommended legislative changes to enable it to be pro-active in requiring the industry to submit paediatric data as part of the registration application.

Implementation of legislative and other mechanisms that require drug companies to study drugs in children and present that information at the time of registration. This strategy is currently in place in the United States of America, however this measure has been successful in the more profitable drugs (see below).

United States experience

The United States Food and Drug Administration introduced a number of regulatory changes in late 1997 requiring manufacturers of new and marketed drugs and biological products to conduct paediatric studies in certain circumstances ('the Paediatric Rule'). A status report to the US Congress in January 2001 summarises the background to these changes and details the achievements to date.[4]

NSW Health has advised the Committee that these policy changes have resulted in a vast increase in the number of drug studies involving children. NSW Health expressed its view to the Committee that similar changes are needed in Australia and worldwide.[5]

What would be the advantages of adopting the US approach in Australia? Is it necessary and feasible?

OFF-LABEL PRESCRIPTION FOR CHILDREN AND YOUNG PEOPLE

The Committee was advised that for many drugs and medications there is considerable clinical experience, and some research evidence, to support their use by children in certain circumstances.

The prescriber is therefore placed in a difficult position in choosing between prescribing in a manner that the product information does not recommend, or withholding a treatment that she or he believes is likely to benefit the child.[6] This type of prescription is commonly referred to as 'off-label' prescribing.

Extent of off-label prescription

The Committee was advised that off-label prescription is widespread and is often based on anecdotal/practical evidence of long use by doctors and it is published in medical journals. For example, the labelling for Ritalin and dexamphetamine is that it is approved for use in children with ADD, or ADD, over six years of age. If you prescribe it to someone under six years of age it is technically off-label, but, the Committee heard many reports of Ritalin prescribed for children under six.[7]

The Committee was also advised that the situation in other countries is not dissimilar. Dr Madlen Gazarian of the Sydney Children's Hospital advised that:

> …in the Netherlands the extent of such 'unlicensed' and 'off-label' prescription has been estimated to be over 90 percent in the hospital setting. … A similar survey in children's hospitals across five European countries, including the United Kingdom, found that almost 50 percent of all prescriptions were either unlicensed or 'off-label', and the situation in Australia is not likely to be any different.[8]

Medico-legal implications?

Note that this 'unapproved' or 'un-recommended' use does not necessarily imply improper or illegal use. Dr Daryl Efron, a paediatrician at the Royal Children's Hospital advised the Committee that:

> '…in fact it is medico-legally defensible if used in accordance with accepted medical practice…'[9]

However, the Australian Association of Paediatric Teaching Centres (**'AAPTC'**) stated that there is:

> '*confusion* about the medico-legal implications among consumers and health professionals who prescribe, supply and administer to children pharmaceuticals unapproved for use in children (emphasis added).'[10]

In this regard the Association has made the following suggestion:

Possible recommendation

That there needs to be clarification of the medico-legal implications of using unapproved pharmaceuticals in children, in particular, distinctions between the unapproved use of approved drugs, contraindications and the use of unregistered drugs.[11]

Off-label prescription and the pbs

The Commonwealth Government's Pharmaceutical Benefits Scheme (**'PBS'**) is outlined in **Issues Paper No. 1**. The Committee was advised that for a drug to be listed on the PBS as having a paediatric indication there must be research evidence to support its safety and effectiveness in children.[12]

The Committee acknowledges the policy position for this requirement. However, it is concerned about the implications of this situation for children and young people and their families because medications that are prescribed off-label for children are not able to be subsidised and therefore are more expensive to obtain.[13]

The Australian Association of Paediatric Teaching Centres has suggested a review of the Pharmaceutical Benefits Scheme and the cost sharing cost-sharing agreements between the Commonwealth and the States, with a view to:

- Facilitating the community provision of pharmaceuticals suitable for children, particularly for chronic diseases of childhood;
- Alleviating the negative financial and convenience factors associated with current dual funding arrangements; and
- Ensuring the needs of children are met by the inclusion of benefits relevant to the treatment of childhood diseases.[14]

Possible risks of off-label prescription

Several submissions to the inquiry from medical practitioners and institutions expressed concern about the prescription of drugs developed for adults for children and young people. This issue relates to all types of drugs. However, submissions drew the Committee's attention to psychotropics and anti-depressants as particular drugs of concern.

For example, the Committee received oral and written submissions from medical professionals expressing concern about the use of off-label medication because they have not been tested in children, in the context of the brain development of young children.[15] The Committee also heard an oral submission from one medical professional who expressed concern that the use of off-label medications for behavioural disorders are possibly of even greater concern that the use of stimulants.[16]

In its submission, the Sydney Children's Hospital summarised the risks for children of the absence of paediatric testing and labelling:[17]

- Inadequate dosing information exposes paediatric patients to the risk of adverse reactions that are potentially preventable;

- Children may be exposed to the ineffective treatment through under-dosing or inappropriate use;

- Children may be denied the benefit of therapeutic advances because physicians are only able to prescribe existing, less effective, medications in the face of insufficient information about a new medication;

- Children may also be denied access to important medications because of a failure to produce drugs in forms that can be used by young children (e.g., liquids or chewable tablets).

The Committee is concerned with the health risks posed to children and young people due to the lack of clinical testing on drugs that are used or can be used in children and young people.

The Committee is also concerned that children and young people may be missing out on an effective treatment as a result of inadequate testing, licensing of drugs and medications.

Even if the practical use of the drug has shown some effectiveness in children, there are difficulties in determining the appropriate dosage for children.

Dr Noel Cranswick at the Royal Children's Hospital in Melbourne has a unit dedicated to the study of medication in children. Their particular concern is prescription and use of medications developed for adults in children and their clinical trials centre will be addressing this matter.

REASONS FOR A LACK OF PAEDIATRIC TESTING

Submission to the inquiry revealed that there three major impediments to conducting clinical testing of drugs and treatments in children. First, ethical issues concerning testing drugs on children; second, a lack of funding for research and clinical trials; and third, deficiencies in the clinical testing system.

Ethical issues

There are ethical considerations which prevent tests being conducted on children. This is particularly due to a potential risk of toxicity in such trials and the difficulty in obtaining informed consent from children to participate in such trials.

In 1999, the National Health and Medical Research Council has produced a 'National Statement on Ethical Conduct in Research Involving Humans'.[18] The statement includes the following information about research involving children:

> Research is essential to advance knowledge about children's and young people's well-being, but research involving children and young people should only be conducted where:
>
> (a) The research in question is important to the health and wellbeing of children or young people;
> (b) The participation of children or young people is indispensable because information available from research on other individuals cannot answer the question posed in relation to children or young people;
> (c) The study method is appropriate for children or young people; and
> (d) The circumstances in which the research is conducted provide for the physical, emotional and psychological safety of the child or young people.
>
> Consent to a child's or young person's participation in research must be obtained from:
> (a) the child or young person whenever he or she has sufficient competence to make this decision; and either
> (b) the parents or guardian in all but exceptional circumstances; or
> (c) any organisation or person required by law.
>
> An HREC must not approve, and consent cannot be given for, research which is contrary to the child's or young person's best interests.
>
> A child's or young person's refusal to participate in a research project must be respected.

Lack of funding for research and clinical trials

The Committee has noted the disparity between the level of funding for research into medications for use in children and for those for use in adults.

For example, over the past five years, NHMRC expenditure for project grants specifically for child-health research has averaged about 1% of its total research expenditure annually.[19] This is of particular concern considering the beneficial impact of effectively conducting and implementing research into practice, such as the decline in the rate of sudden infant death syndrome (SIDS) in Australia after intervention campaigns to reduce prone sleeping position in infants.[20]

The Committee is aware that there is little incentive for the pharmaceutical industry and for research institutes to invest in expensive large scale clinical trials to prove that these medications are safe and effective in children and to invest in licensing. For example, drugs for diseases that are common in adults but rare in children such as kidney disease are rarely tested on children.

The current system of clinical trials in paediatrics seems to favour more heavily the market benefits for the pharmaceutical industries rather than the potential health benefits of these pharmaceutical products to children and young people.

The pharmaceutical industry may play a pivotal role in the many research areas identified as lacking in relation to the use of drugs and medications, as well as in educating the community about the safe use of drugs and medications. Representatives of the industry are often involved in policy making with the Commonwealth Government, and particularly in

areas that directly relate to the market interests of pharmaceutical companies. The Committee believes the industry should be encouraged to participate for fully in all aspects of policies and strategies relating to the use of pharmaceuticals, and recommends that such strategies are encouraged at State levels.

Possible recommendation

That the pharmaceutical industry be encouraged to participate for fully in all aspects of policies and strategies relating to the use of pharmaceuticals, and that such strategies should be encouraged at State levels.

Deficiencies in the clinical testing system

There are difficulties in organising clinical trials in children, particularly in relation to recruiting paediatric patients and centers and developing appropriate formulations (e.g., suspensions that children can swallow).

There is also a lack of consistency with regard to the definition of an upper age limit of a 'child'. Prescribing information reflects the age ranges of clinical studies as opposed to any biological/pharmacokinetic logic.

The Committee also heard of the failure in some cases to submit available paediatric data to the regulatory authority.

IMPROVING RESEARCH INTO DRUGS FOR PAEDIATRIC USE

Incentives

It has been suggested that registration incentives and market incentives should be provided to pharmaceutical and research centres to conduct clinical trials of products for use in children and young people, and that inducement and support is provided to the industry and research organisations for the training and career support for paediatric pharmacology.

Support for research into paediatric pharmacology

This could involve the establishment and promotion of a network of centres and research institutes with expertise in the design and conduct of clinical trials in children that would be developed and work with the close cooperation between regulatory authorities and the pharmaceutical industry. This network could also be supported by (or work together with) paediatric centres and research funding organisations.

An alternative approach could involve the setting up of Paediatric Pharmacology Research Units modelled on current practice in the United States of America that are specifically charged and funded to undertake research in use of medications in clinical paediatry.

Monitoring and reporting

As well, the establishment of monitoring and reporting mechanisms in hospitals for adverse effects of medications and treatments in children and young people with a system of reporting that would be closely coordinated by the Adverse Drug Reaction Advisory Committee has been suggested.

These monitoring and reporting mechanisms should include data relating to therapeutic use of drugs and medications, accidental administration of pharmaceuticals, adverse effects due to a combined use of pharmaceuticals and complementary medicines etc.

The establishment of such mechanisms should allow the routine collection of knowledge and experience in the professional use of 'off-label' drugs that have not been trialled on children but which are used on children and allow the organisation of this information into a guide for clinicians.

Closing the gap between what is known about a drug and what is reflected in the Product Information

A further way to address this problem is to develop guidelines to ensure that the post-marketing surveillance of drugs and medications is appropriately recorded in the Product Information (the registration name and details). For example, government regulatory agencies could include details in the Product Information that have been gathered through research and experience after the drug has been registered.

Another proposal is for legislative requirements to be developed, similar to those of the US National Institute of Mental Health, that require that before receiving funding for pharmacological or clinical drug trial research, researchers would have to explain or justify why they have not used a range of peopleXto change the current practice of testing mostly on middle-aged white men and women.

[1] For example, Submission 9, Mr Stan Stanfield; Submission 20, Mr Henry Bartinik; Submission 54, Dr Daryl Efrom, Paediatrician, Centre for Community Health, Royal Children's Hospital, Melbourne; and Submission 77, Mr John Murray and Ms Kath McFarlane, The Positive Justice Centre.

[2] Submission 20, Mr Henry Bartnik; and Submission 77, Mr John Murray and Ms Kath McFarlane, The Positive Justice Centre.

[3] Australian Drug Evaluation Committee, *Report of the Working Party on the Registration of Drugs for use in Children*, October 1997. Note that the ADEC is part of the Therapeutic Goods Administration.

[4] Department of Health and Human Services US Food and Drug Administration. *The Paediatric Exclusivity Provision. January 2001 Status Report to Congress*. This report ca be viewed at: www.fda.gov/cder/pediatric/reportcong01/pdf

[5] Submission 79, the Hon Craig Knowles MP, Minister for Health.

[6] Submission 54, Dr Daryl Efron, Paediatrician, Centre for Community Health, Royal Children's Hospital, Melbourne.

[7] Evidence from Dr Daryl Efron, Consultant paediatrician, paediatrics and Child Health Division of the Royal Australian College of Physicians, Royal Children's Hospital, Melbourne, 11 September 2001, p 45.

[8] Submission 66, Dr Madlen Gazarian, Senior Lecturer, School of Women's and Children's Health, University of NSW, Sydney Children's Hospital, p 1.

[9] Submission 54, Dr Daryl Efron, Paediatrician, Centre for Community Health, Royal Children's Hospital, Melbourne, p.40.

[10] *Policies 1997, Pharmaceuticals for Children*. The Australian Association of Paediatric Teaching Centres, 1997, 5.

[11] *Policies 1997, Pharmaceuticals for Children*. The Australian Association of Paediatric Teaching Centres, 1997, p 7.

[12] Evidence from Dr Daryl Efron, Consultant Paediatrician, Centre for Community Health, Royal Children's Hospital, Melbourne, 11 September 2001, p 40.

[13] Evidence from Dr Daryl Efron, Consultant Paediatrician, Centre for Community Health, Royal Children's Hospital, Melbourne, 11 September 2001, p 40.

[14] *Policies 1997, Pharmaceuticals for Children*. The Australian Association of Paediatric Teaching Centres, 1997.

[15] Evidence from Associate Professor Florence Levy, Avoca Clinic, Prince of Wales Hospital, 10 September 2001, p 16.

[16] Evidence from Associate Professor Florence Levy, Avoca Clinic, Prince of Wales Hospital, 10 September 2001, p 15.

[17] Submission 66, Dr Madlen Gazarian, Senior Lecturer, School of Women's and Children's Health, University of NSW, Sydney Children's Hospital, p 1.

[18] NHMRC, *National Statement on Ethical Conduct in Research Involving Humans*, Commonwealth of Australia, 1999The statement can be viewed at: http://www.health.gov.au/nhmrc/publications/synopses/e35syn.htm

[19] Gazarian, M, 'EBM in Practice: Paediatrics', *MJA* Vol.174, 4 June 2001.

[20] Gazarian, M, 'EBM in Practice: Paediatrics', *MJA* Vol.174, 4 June 2001