

**OFF-LABEL USE OF MEDICINES IN THE PAEDIATRIC POPULATION:
RECOMMENDATIONS FOR ASSESSING APPROPRIATENESS**

Discussion Paper for Consultation

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1. INTRODUCTION

The majority of marketed medicines world-wide, including those commonly used or which could potentially be used in the paediatric population, have not been studied in the relevant paediatric age groups and so are not approved by drug regulatory authorities for use in children. The reasons for this situation are complex and are discussed in detail elsewhere. (1) (2) (3) (4) It is estimated that currently at least three quarters of all prescription medicines lack sufficient information on paediatric use in the product label, and this is most marked in the younger age groups. (4, 5) This situation has led to the widespread practice of prescribing “unapproved” (“off-label” or “unlicensed”) medicines in the paediatric population, with rates above 90% in some settings.

Recent legislative and regulatory initiatives in the US have resulted in more medicines research in children. While this has led to improvements in licensing of some medicines for older children in the USA, (6) the impact on product labeling in other parts of the world and for younger children has so far been small or lacking.(5) Similar initiatives have recently been introduced in the European Union and may eventually reduce the need to consider prescribing “unapproved” medicines in most children. However, it is likely to be some time before the full impact of these combined initiatives are reflected in the amount and quality of evidence available to inform therapeutic decisions in the paediatric population at a global level.

While “off-label” medicines use is not illegal, and may sometimes be appropriate, it is associated with important clinical and ethical concerns which need to be considered when assessing overall benefits and risks.(7) In some countries, promotion of off-label uses by pharmaceutical companies is prohibited. However, off-label prescribing by clinicians is otherwise an area of practice that is not regulated by drug regulatory authorities, neither in general terms nor specific to individual medicines. Traditionally, paediatric prescribers have been expected to use their “professional judgements” to determine the appropriateness of such prescribing in individual patients(8) but with often limited data to inform and no explicit guidance in exercising such judgements.

The objectives of this paper are to:

1. Summarise the extent of off-label use of medicines in the paediatric population globally;
2. Review how various medicines selection bodies and guideline developers have approached the question of off-label medicines use in the paediatric population; and
3. To make recommendations about:
 - how WHO should assess the suitability of medicines proposed for addition to the Essential Medicines List (EML) for Children if these are currently not registered by competent regulatory authorities for the specific indication proposed; and
 - what evidence should be sought and how it should be presented if an off-label use is to be advocated by WHO in such a manner.

Although this paper will address the needs of decision makers with regard to developing a Model Essential Medicines List for Children in the first instance, the general concepts and recommendations are intended to inform the wider spectrum of therapeutic decision-making in the paediatric population globally.

2. DEFINITIONS

Off-label prescribing refers to prescription of a registered medicine for a use that is not included in the product information (PI) or that is disclaimed in the PI.(9, 10) Examples include use in a different indication, age group, dose, frequency or route to that which is approved by regulatory authorities (see Table; examples relate to regulatory approval status in Australia, unless otherwise indicated)

Table: Examples of off-label medicines use

Reason for off-label use	Example
Indication	<ul style="list-style-type: none"> • quinolone antimicrobials used to treat bacterial gut infections or severe neonatal infections in the developing world • azithromycin used for anti-inflammatory effect in cystic fibrosis
Dose	<ul style="list-style-type: none"> • use of adult formulations (e.g. tablets) in fractions (e.g. ¼ or 1/8th tablet), leading to dosing outside the approved paediatric dose in mg/kg • once daily dosing of gentamicin in children
Age	<ul style="list-style-type: none"> • valaciclovir used in children under 12 years • intravenous paracetamol use in neonates
Route	<ul style="list-style-type: none"> • diazepam injection administered rectally for treatment of status epilepticus

An *unlicensed* or unregistered medicine is a medicine or dosage form of a medicine that has not been evaluated nor approved by the regulatory authorities. These include medicines whose formulation is modified (eg extemporaneous preparations); those that are imported before a license has been granted; or those that are chemicals used for therapeutic purposes.(10)

There is considerable variability in the published literature in terms of how the terms “off-label”, “unlicensed” or “unapproved” are defined and used in different studies.(10) For example, the use of “extemporaneous” formulations where modification of a registered product has occurred (e.g. pharmacy compounded formulations, such as preparation of a liquid suspension from crushing tablets or capsules and/or addition of diluent and/or flavouring agent) is considered “unlicensed” by some (9, 10) whereas others include it in the category of “off-label” use.(4) This definitional difference is an important distinction that should be better clarified, as the legal status of off-label and unlicensed uses is not the same.

In some countries, unlicensed uses may be considered illegal unless specific approval has been sought from the drug regulatory agency (e.g. to import a paediatric formulation from another country where it is approved).

In terms of determining appropriateness of use, these terms are not so meaningful on the global stage as they refer to the regulatory approval status of a medicine in a particular country. This status can vary between countries for a variety of reasons that are independent of the scientific evidence to support particular uses (e.g. different regulatory standards or skills, different marketing incentives for pharmaceutical companies in different countries). So, in essence, the regulatory approval status is a “surrogate” for the issue of real interest, which is the availability of valid scientific support for a particular use in the paediatric population.

3. EXTENT OF UNAPPROVED MEDICINES USE IN THE PAEDIATRIC POPULATION

Much has been published about the extent of, and problems associated with, the off-label and unlicensed use of medicines in the paediatric population, as recently summarised by several authors.(10, 11) Most paediatric studies have evaluated the extent of both off-label and unlicensed uses. In view of the definitional variations in the published literature and the need to assess the extent of overall “unapproved” uses of medicines in the paediatric population, studies addressing both “off-label” and “unlicensed” uses are included in this summary.

Prescribing of “unapproved” medicines (i.e. off-label or unlicensed as defined above) is widespread in the paediatric population across a variety of settings. The majority of published studies are from European countries, with a few from other countries in the developed world (e.g. US, Australia, Israel). The bulk of these studies are in hospitalised children, demonstrating that between 36-92% of hospitalised paediatric patients receive at least one “unapproved” medicine during their hospitalisation.(10) Higher rates are observed in younger age groups, such as neonates (80-97%), and in sicker patients (70-92% in paediatric ICU). Fewer studies have examined the extent of “unapproved” prescribing in the community setting, but these indicate an overall lower rate of such use in the community (16-56% of children) versus hospital setting. The overall rates of prescriptions considered off-label or unlicensed ranged from 11-80%.(10) The most common reason for off-label use was dosage and the most common types of medicines used in an off-label or unlicensed way included analgesics and anti-asthma medications.(10) Factors associated with off-label use in the community setting include new drug; younger age; specialist treatment; and low use drug.(12)

There are no similar published studies evaluating the extent of off-label or unlicensed medicines use in the paediatric population in the developing world setting. This could suggest either a lack of awareness or interest about this issue amongst health care professionals in the developing world.(13) If true, such lack of prescriber awareness would be of great concern as it might mean that children’s exposure to suboptimal therapies in developing countries may be even greater, especially if the promotion of off-label uses by

pharmaceutical companies occurs routinely as reported by some authors.(13, 14) The well-known and extensive problem with counterfeit medicines in the developing world will not be addressed here.

Although the PI may be the main reference for many prescribers, in some cases the best available evidence may not be reflected in the PI, (15, 16) so off-label yet evidence-based prescribing may be the more appropriate choice.(17) This may be due to new evidence becoming available after marketing (as there is currently no provision for regular updating of the PI in most countries) or lack of incentive for the sponsor to seek extension of labeling. However, in the majority of cases adequate research evidence to support off-label prescribing may be lacking. A recent survey of 150 million off-label prescriptions in the US found most (73%) had little or no scientific support, even when sources other than the PI were searched.(18) Thus, only a small proportion of off-label prescribing may be justified by scientific evidence. Interestingly, the vast majority of the studies evaluating the general extent of off-label prescribing in the paediatric population have so far not systematically examined this question and so the overall proportion of “unapproved” uses in the paediatric population that may be well supported by scientific evidence is currently unknown. Some paediatric studies have examined this question in a limited way (e.g. in certain patient groups, or using local treatment guidelines as the standard)(19-21) suggesting that off-label/unlicensed uses generally correspond with recommendations in relevant drug therapy resources. However, it is difficult to generalise such data to a broader paediatric population due to the non-standard definition of “appropriateness” and lack of a widely accepted medicines information resource that defines evidence-based therapies (including, but not limited to, standard dosing information) for paediatric patients globally.

Prescribing medicines “off-label” is clearly widespread in paediatrics, not illegal, and in some cases represents best practice. However, it does bypass the safeguards of the drug regulatory process and places a greater onus of responsibility on the individual prescriber to assess the benefits and risks of such use for an individual patient. While this may be acceptable as an exception, it is clearly unacceptable when it becomes the norm.(1, 22) The main advantage is not denying children the potential to benefit from new medicines. Such use may be clinically appropriate (e.g. exceptional use in an appropriately informed patient with serious disease, when there are no alternatives, and potential benefits outweigh potential risks).(7) However, it may also be associated with a number of potential risks, some of which appear to be less well recognised or appreciated by health professionals and parents/carers.(23)

An often-repeated phrase is that “children are not little adults”. There are important pharmacokinetic (PK) and pharmacodynamic (PD) differences between children and adults (and between different age groups within paediatrics) resulting in differences in both the beneficial and harmful effects of medicines in these populations. In addition, some effects may only be able to be observed in the paediatric population due to the unique aspects of childhood (e.g. effects on growth and development) or because of the different diseases that may only affect this population (e.g. neonatal respiratory distress syndrome). Certain adverse drug reactions may only occur in the paediatric population, some of which may be related to known PK differences (e.g. chloramphenicol and grey baby syndrome), with others occurring without a clear underlying mechanism and so less predictable without

clinical studies (e.g. aspirin and Reye syndrome). Therefore, use of a medicine with no (or suboptimal) evidence about efficacy, safety and appropriate dose in the paediatric population may expose children to ineffective therapies and to unknown risks of adverse events. The lack of appropriate paediatric formulations (e.g. liquids) for unapproved medicines presents a further safety risk, as the preparation of extemporaneous formulations is not subject to standard quality assessments, with uncertain and variable bioavailability and stability.

4. CONSEQUENCES OF UNAPPROVED MEDICINES USE IN THE PAEDIATRIC POPULATION

The health outcomes of unapproved medicines use in the paediatric population are not systematically evaluated, compounding the original problem by further limiting the evidence base for future treatment decisions. This is especially so for safety outcomes, with gross under-reporting of adverse drug reactions (ADRs), which may be even more pronounced for unapproved vs. approved uses of medicines. However, there is now accumulating evidence of resulting harm, with increased incidence and seriousness of adverse drug reactions associated with off-label and unlicensed medicines use in children.(11, 24) Spontaneous reports to the EMEA database from 2002-2004 showed 820 suspected serious ADRs in children receiving an unapproved medicine, 130 of which were fatal and 361 of which resulted in or prolonged hospitalisation.(24) Another study of spontaneous ADR reports in Swedish children over a one year period identified 158 ADRs, of which 42.4% occurred with off-label use; these were more frequently serious rather than non-serious ADRs and were mostly due to use in a non-approved age or dose.(25) There are few studies that enable an accurate measure of the magnitude of the problem to be derived; one prospective evaluation of community paediatricians' prescribing found off-label prescribing to be significantly associated with ADRs, with a relative risk of 3.44 and this increased to 4.42 when the off-label use was for an indication not included in the label for adults.(26) Another study of hospitalised children also found an increased risk, with 6% of off-label prescriptions vs. 3.9% of approved uses being associated with ADRs.(27) The review by Cuzzolin et al(11) found that overall 23-60% of off-label or unlicensed prescriptions were associated with an ADR.

To add to this accumulating evidence, some long-established and well-accepted off-label uses have been shown to either be ineffective or harmful when subjected to prospective evaluation as part of the recent US initiatives stimulating increased medicines research in children;(4, 28) e.g. deaths associated with propofol used for sedation in the paediatric intensive care setting. New dosing and or safety information on an increasing number of medicines used in the paediatric population (e.g. midazolam, fluvoxamine, gabapentin, etodolac, ribavirin and interferon alfa-2b, topical betamethasone, pimecrolimus, sevoflurane) have also emerged through this mechanism. (4, 28)

Additional and broader consequences that need to be borne in mind are that widespread acceptance of off-label prescribing may itself be contributing to perpetuating the problem of children having limited access to high quality medicines. This may be occurring through any

or all of the following mechanisms and there are some (limited) data to support each possibility:

- Limitation of the needed research agenda: If there is existing (or anticipated) widespread use in the paediatric population, the incentive for the pharmaceutical industry to properly evaluate benefits and risks specifically for paediatric use would be reduced or removed. Furthermore, if clinicians have formed an opinion (based on anecdotal experience rather than unbiased scientific research) that a medicine is likely of benefit, then they would have lost “ equipoise”, which is a necessary requirement for enrolling patients in any future randomised clinical trials, whether investigator initiated or sponsored by the pharmaceutical industry. Similar beliefs by parents and children may also limit their willingness to participate in appropriate clinical trials, so that the needed evidence may never become available.
- Withdrawal of useful (older, approved) medicines from the market because of reduced demand if there is widespread use of a newer (unapproved) medicine in the paediatric population without demonstration of a clear advantage over the older alternative. This results in a “double disadvantage” of loss of access to a medicine with demonstrated effectiveness/safety and increasing use of one without such evidence in the paediatric population.(29)
- Public funding of unproven therapies or those with suboptimal scientific support may represent wasteful use of scarce resources. It may be that investment of at least a proportion of funds intended to provide access to “essential” medicines may be better directed at supporting the needed research. This may be a more cost-effective use of these resources and such an approach would benefit from further discussion, especially for meeting the needs of children in the developing world. (Alternatively, children may be denied easy access to medicines that are “unapproved” by regulatory authorities but are of proven benefit based on available scientific evidence since most funders rely on regulatory approval status to inform their decisions).

5. CURRENT APPROACHES TO DETERMINING APPROPRIATENESS OF OFF-LABEL USES

In contrast to the available literature about the extent and consequences of off-label prescribing, there has been virtual silence in terms of specific guidance to assist clinicians, guideline developers and policy makers trying to make decisions about the appropriateness of such prescribing. Most clinicians perceive off-label prescribing as appropriate and that the benefits outweigh the risks.(30) However, their awareness of consequences appears to be minimal, with a worryingly low level of concern about risk of side effects, unevaluated efficacy and issues surrounding informed consent.(23) This raises questions about the validity of their risk: benefit analysis when making decisions about off-label prescribing.

Recent legislative and regulatory initiatives in the United States and more recently the European Union have provided incentives and inducements for the pharmaceutical industry to undertake more medicines research in children. Eventually these initiatives may reduce the need to consider off-label prescribing in many instances.(28) Until such time, practitioners are expected to “use their professional judgement” to determine the appropriateness of off-label use in individual patients.(8) However, no explicit guidance in exercising such judgement is available. In addition, the legal and ethical ramifications of such prescribing appear to be a source of confusion, with variability in opinions and practice amongst prescribers and professional organisations.(8, 31, 32)

Prescribers may seek advice from a variety of resources providing prescribing information for the paediatric population, including for “unapproved” uses. These may be in the form of medicines compendia (general or paediatric specific), therapeutic guidelines or health technology assessments. Examples include the British National Formulary for Children (BNFc)(33); the Australian Medicines Handbook and Therapeutic Guidelines in Australia; and various consensus statements from the American Academy of Pediatrics Committee on Drugs. In addition, various professional bodies may issue guidelines recommending off-label uses of medicines and most large paediatric hospitals produce local pharmacopoeias providing varying levels of information on “unapproved” uses of medicines in the paediatric population. Some key national bodies producing or commissioning evidence-based guidance to support rational medicines use, such as the National Institutes of Health and Clinical Excellence (NICE) in the UK, the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Agency for Health Care Research and Quality (AHRQ) in the US, do not make recommendations about off-label uses of medicines.

For those organisations that do provide information about off-label uses, there does not appear to be an explicit or consistent process by which recommendations are developed. Most use a combination of scientific evidence and “consensus” opinion of experts. However, to what extent a particular recommendation is informed by evidence vs. opinion is often not explicitly stated. Furthermore, the process and rigour with which scientific evidence is evaluated or consensus is systematically developed, let alone how these components are integrated to form an overall recommendation, is also not explicit for most. For example, the developers of the BNFc state that the information it contains is...

“...based on a survey of clinical literature, longstanding hospital formularies, and national guidelines. Expert advisors throughout the UK have validated the information, and their extensive clinical experience has provided a practical focus. Supervision of the whole process by a formulary committee (doctors and pharmacist closely involved with paediatric care) ensures a system of checks and balances, and consensus”(33)

There is often variability in the recommendations made in different resources (including those within the same country), especially regarding paediatric doses.(34) This likely reflects the unspecified variability in the various decision-making processes that are being used. Such variability also extends to decision-making by funders of health care with regard to reimbursement for off-label uses of medicines.(35) Clearly, any inappropriate influence or links with the pharmaceutical industry and those involved in making such recommendations or decisions would have major health and financial consequences for the community. Several authors have alleged that such influence applied for at least one widely used drug information resource in the US which made a larger number of positive recommendations for off-label uses compared to resources which did not have such links.(36, 37)

Recently a more explicit process for evaluating the appropriateness of off-label medicines use was described by an Australian organisation which produces independent, evidence-based and consensus guidance for hospital based prescribers and Drug and Therapeutics Committees (New South Wales Therapeutic Advisory Group, NSW TAG).(7) This process helps to more explicitly distinguish between off-label use that can be *justified by high-quality evidence* and innovative therapy that may be justified in individual clinical circumstances (*exceptional use*) or that should be pursued in a *research* context (see Figure). This process is also the first to acknowledge that not all categories of off-label use carry the same level of risk, and to make explicit recommendations for the type of patient consent process that might be appropriate for the different categories of off-label use (see Figure). If there is no high quality evidence supporting use, and the medicine is not suitable for exceptional or research indications, its use is generally not recommended.

Figure: Assessing appropriateness of off-label medicines use
 [reproduced, with permission from MJA 2006;185:544-548](7)



For a detailed analysis of the legal and ethical dimensions associated with consent and the administration of off-label medicines, see Appendix 4 of "Off-Label use of registered medicines and use of medicines under the personal importation scheme in NSW public hospitals: A Discussion Paper"
http://www.ciap.health.nsw.gov.au/nswtag/publications/otherdocs/off_label_use_registered_medicines.pdf

The NSW TAG recommendations provide a systematic approach to guide clinicians and policy makers in evaluating the appropriateness of medicines proposed for off-label use in the paediatric population, with a number of resulting benefits:

- 1) By helping to distinguish more explicitly between off-label medicines use supported by scientific evidence versus innovative therapy, they should help promote evidence-based prescribing;
- 2) Limiting off-label use of medicines to situations where it is justified by pre-specified criteria will support appropriate uses, while helping to reduce or eliminate inappropriate uses (including those which may be inappropriately promoted by the pharmaceutical industry).(38) This will also enhance safety by reducing children's exposure to unnecessary risk;
- 3) A more explicit process for patient consent will help address ethical concerns by better informing children, parents and carers about the benefits and risks associated with "innovative" therapy. This may also help improve their ability to balance the benefits and risks of such medicines use as "therapy" against the benefits and risks of participation in high quality research studies. A careful analysis of these benefits and risks should lead most to conclude that, in general, participation in a clinical trial would provide greater protection and benefits for their child (and the population of children) than with most instances of "innovative" off-label treatment; (6)
- 4) The systematic identification of gaps in knowledge in areas of clinical need will help drive an appropriate research agenda, which in turn should result in more useful new knowledge to inform future treatment decisions. This incentive from the clinical interface (i.e. demand for the better evidence to inform practice) should help complement the various regulatory incentives in the US and EU for stimulating the needed paediatric medicines research. There has been a vast increase in paediatric medicines research in the US resulting from the regulatory initiatives over the last decade.(4, 6) This provides evidence that at least some of the historically quoted barriers to paediatric medicines research (e.g. ethical, scientific, practical) may be more perceived than real, or relative rather than absolute, and that such research can be done when the appropriate drivers are present (e.g. demand by regulators) and financial and practical barriers are addressed (e.g. adequate resourcing of the needed medicines research). Adding demand from health professionals to these drivers should hopefully steer the research agenda in a direction that is more likely to meet children's actual health needs. This will be especially relevant for meeting the needs of children in the developing world.
- 5) These recommendations may be useful when making decisions about the allocation of scarce health resources and help promote cost-effective medicines use.

A major Academic Medical Centre in the US has recommended a similar strategy to support a systematic approach to the evaluation of proposed innovative off-label uses of medicines.⁽³⁹⁾ Additional aspects of the standard process recommended by this group include assigning approved off-label uses to one of three grades (A, B, C) based on the level of supporting evidence and to request prospective outcome evaluation and review of efficacy, safety and cost outcomes for uses approved with the lowest level of supporting evidence (Level C).

This type of approach is also in keeping with the general process that the US Medicare Evidence Development and Coverage Advisory Committee (MedCAC) uses in evaluating the evidence when making decisions about reimbursement policies. If the advice from MedCAC is that a practice has “insufficient evidence” to support outright coverage, the Centers for Medicare and Medicaid Services (CMS) has a number of options it can choose from. These include:

- directly supporting more research to generate the needed evidence;
- approving coverage as long as use occurs only within a clinical trial or similar protocol, thereby providing access to a promising technology while collecting a body of evidence; or
- Make a coverage decision based on the best interpretation of the available evidence.

(see <http://www.cms.hhs.gov/FACA/Downloads/recommendations.pdf>)

The NSW TAG recommended type of decision-making process and that recommended by these US bodies is highly relevant to the WHO in terms of assessing suitability of “unapproved” medicines for listing on the EML. The types of evidence that should be sought and how these should be evaluated and formulated into recommendations for listing on the EML will be discussed in greater detail in the next section. Since the EML is predominantly concerned with making recommendations about medicines use in diseases of high prevalence in the paediatric population, the category of “exceptional use, justified by individual clinical circumstances” will be less relevant at a population level but would still be appropriate to decision making at an individual level.

6. ASSESSING APPROPRIATENESS: EVALUATION OF EVIDENCE

RECOMMENDATIONS

At a global level, deciding whether use of a particular medicine in the paediatric population is appropriate should revolve around answering the question “*Is there high quality evidence supporting its use in the paediatric population*”, rather than on its regulatory approval status in a particular country. It is also worth noting that while data supporting regulatory approval is useful, it does not usually provide sufficient information to support therapeutic decision making in all clinical contexts,(40) as discussed below.

The answer to this question should be derived from a critical evaluation of the best available patient-based research evidence about *clinical effectiveness* and *safety*, ideally from clinical studies conducted in the relevant paediatric population (and ideally using age-appropriate paediatric formulations of high quality). The overall aim is to determine whether a particular medicine has an overall favourable *benefit vs. risk* ratio to justify any use in children, at an individual or population level. In order to justify routine and widespread use, additional information about *cost-effectiveness* for the relevant context in which use will occur is also needed. If a number of alternatives are available to treat a particular condition (including newly marketed medicines), evidence from comparative studies should be sought and the medicine with a *demonstrated advantage* in clinical effectiveness and/or safety and/or cost-effectiveness over other available alternatives should be chosen as the preferred agent for routine use.

Some of the needed information may be obtained from drug regulatory agencies and information in drug labels (e.g. efficacy and limited safety information) from competent authorities (e.g. FDA, EMEA). The lack of such labeling information, however, would not necessarily mean that the evidence does not exist and so the published literature (or other valid sources) should be searched to locate relevant studies of effectiveness and safety in the paediatric population. Available high quality evidence from anywhere in the world could inform decisions about use at a global level, unless there are valid reasons (e.g. important genetic, racial differences) to seek evidence from studies conducted in specific regions or in specific populations.

Information about *comparative* clinical effectiveness/safety and cost-effectiveness will need to also be sought from the published literature (or other valid sources) as these considerations, which are fundamental to rational use, are generally not within the remit of drug regulatory agencies and so are not part of assessments for marketing approval.(40)

The assessments referred to above should be primarily informed by appropriate high quality scientific *evidence*. However, expert *judgements* will need to be exercised in order to decide what type of evidence might be appropriate for a given health issue or context; to evaluate its validity as well as to interpret its clinical meaningfulness and decide on its applicability to relevant paediatric health issues and contexts. *The people and processes through which such assessments are conducted to ensure that sound decisions are ultimately reached will need to be carefully discussed and explicitly defined (see section 8).*

Evaluating effectiveness

The level of rigour of this evaluation should be similar to that used by competent drug regulatory agencies (e.g. FDA, EMEA) for the clinical evaluation of medicines submitted for marketing approval. Important considerations include the *types* of studies (e.g. RCT, observational, or PK, PD); the *quality* of the study (independent of study type); the *validity* and *strength* of evidence; and its *applicability* to the relevant paediatric population (e.g. defined by different ages or disease states). Accepted guidelines for critical appraisal of therapeutic studies, for grading of “strength of evidence” and for deciding about applicability of research evidence to different patient circumstances can be used in answering this question.(41) (42)

The randomised controlled clinical trial (RCT) is widely accepted as the gold standard study design for determining the effectiveness of interventions, with some exceptions.(43) While high quality RCTs remain the ideal, they do have a number of acknowledged limitations, especially those performed specifically for gaining marketing approval.(40) These include relatively small numbers of included subjects (especially in published paediatric RCTs(44)) and short duration of follow-up, both of which limit their usefulness in determining effectiveness (and safety), especially in the treatment of chronic childhood conditions. In addition, subjects included in RCTs are often homogeneous and results may not be generalisable to the general paediatric population. A particular example of this is the issue of the different age groups that are encompassed by paediatrics (neonates; infants; children; and adolescents). There are large variations in drug handling and response between these age groups and so studies conducted in the relevant age groups are needed to inform decisions about medicines intended for use in that age group. Systematic reviews of RCTs may be able to overcome some but not necessarily all of these limitations.

A number of innovative trial designs have been developed to facilitate the study of small numbers of patients, which are particularly relevant for the study of uncommon or rare but serious childhood diseases. These include adaptive designs, such as Bayesian sequential studies;(45) randomized withdrawal designs;(46) the randomized placebo phase design;(47) and “n of 1” studies for populations.(48) Some of these study types may offer additional advantages over traditional RCTs, such as helping determine optimal patient and dose selection. Studies using such designs have been conducted in the paediatric population and should be sought to inform treatment decisions where available. While such studies are currently not numerous, it can be anticipated that their number is likely to increase in the future as more paediatric medicines research networks are established and become operational to address the increasing demand for better evidence about medicines for use in the paediatric population.

Another important aspect of assessing effectiveness is whether outcomes that are clinically meaningful to the paediatric population have been evaluated in a particular study.(49) These may include patient-based outcomes such as symptom scores or quality of life measures (validated in the relevant paediatric population) or paediatric specific ones, such as developmental, learning and behavioural outcomes. In some cases, a well designed and conducted observational study (e.g. prospective cohort study) evaluating clinically meaningful outcomes at relevant time points may be preferable to a RCT that does not

possess these features.(50, 51) Cost-effectiveness may also be usefully assessed in high quality observational studies.(52) Although the role of observational studies in the evaluation of treatments has been a long-standing point of controversy,(53) judicious use of data from high quality observational studies to address relevant clinical questions (e.g. assessing effectiveness in real-life settings vs. efficacy under ideal circumstances; and meaningful safety assessments, see below) will be important. The need to explore the potential of alternative valid methodologies to investigate the safety and efficacy of new drugs under certain circumstances(54) is a persuasive argument that is especially relevant for the paediatric population.

Finally, regulatory agencies such as FDA and EMEA make provision for extrapolation of efficacy data from clinical studies in adults when certain specific conditions and assumptions are met. For example, if similar systemic exposure in adult and paediatric patients can be assumed to produce similar efficacy, then only PK data from the relevant paediatric population may be needed to allow extrapolation of efficacy data from clinical studies in adults. Where the existence of such PK and clinical effect relationships are clearly demonstrated, use of such data seems reasonable. However, such relationships may be more often assumed rather than demonstrated and so caution is recommended in judging the validity and applicability of this type of data. This caution is especially pertinent to any extrapolations about safety since many adverse drug reactions (especially the more serious ones) are not dose related and so would not be expected to be correlated with systemic drug exposures. Furthermore, as has been previously discussed, medicines may have a very different adverse reaction profile (type and frequency) in the paediatric population. These may be due to unpredictable mechanisms and so could only be detected through relevant clinical studies.

Evaluating safety

RCTs also have a number of limitations with regard to safety evaluation. First, as referred to above, the relatively small numbers of subjects in most RCTs mean that only the more common types of ADRs have any chance of being detected, even in a high quality RCT. For example, in order to be able to detect an ADR that might have an occurrence rate of 1 in 500, approximately 1,500 subjects need to have been exposed in order to have 95% probability of detecting that event.(55) Most paediatric RCTs are considerably smaller in size(44) and so do not have much chance of being able to detect uncommon or rare ADRs, some of which may be severe or serious and have major impact on treatment decisions if known. Second, the limited duration of most RCTs mean that ADRs that may be related to prolonged exposure or cumulative dose as well as those that may have delayed or latent onset will also not be detected. This issue is especially relevant in paediatrics as many medicines are used long term (e.g. anti-asthma medicines, treatments for ADHD) or in periods of continuing organ development (e.g. younger children) and so data about safety outcomes, especially on paediatric relevant outcomes (e.g. growth, neurodevelopment, school performance) in typical patterns of use are crucial to inform treatment decisions. Third, evaluation of relevant safety outcomes in most RCTs is much less rigorous and complete than efficacy outcomes,(56) so even common ADRs that do have a good chance of being detected may not be. Finally, all of these inherent limitations in design are further compounded at the reporting stage, with evidence indicating that there is selective reporting of outcomes in

most RCTs, leading to an overestimate of benefits vs. risks of a particular intervention.(57)
This is especially so with RCTs that are sponsored by the pharmaceutical industry.(58)

Existing guidelines and systems for ranking evidence are also focused mostly on efficacy evaluation and so RCTs are considered the highest quality study design. However, the types of studies that should be sought with regard to evaluating the full spectrum of safety of a particular medicine are broader. In many instances only observational studies (e.g. cohort or case-control studies) from post-marketing surveillance, rather than randomized controlled trials, or meta-analyses, will provide the necessary data. This applies particularly to rare, but potentially serious, adverse effects (e.g. serious sepsis and death associated with anti-tumour necrosis factor therapy) or those which manifest following prolonged exposure (e.g. growth retardation with steroids) or following a long latent period (e.g. infertility following cancer chemotherapy in childhood).

Therefore, in order to build a *composite* picture of the overall safety profile of a particular medicine in the paediatric population, evidence from a number of different sources needs to be collated. These sources will include RCTs (published and unpublished), systematic reviews, observational studies (e.g. cohort and case control) as well as information from post-marketing surveillance (including voluntary ADR reporting systems and database linkage studies). This type of systematic collation of safety information is a very important step in both the initial and ongoing evaluation of the overall benefit vs. risk and appropriateness of use (approved and unapproved), but is currently not occurring systematically, especially for unapproved medicines used in children. Addressing this unmet need will be even more important in the current climate of increased medicines research in certain parts of the world, sometimes revealing important safety information, but not necessarily reflected in regulatory approval status or paediatric prescribing information available in other parts of the world in a timely way. It is increasingly recognised that knowledge about the risks and benefits of a medicine changes over its lifetime and must be better understood in order to ensure patient safety.(59)

Determining overall benefit vs risk: Overall recommendations

Routine use of a particular medicine (including its listing on the EML) could be justified if there is high quality evidence supporting clinical effectiveness, and sufficient evidence regarding the medicine's safety profile to suggest an overall reasonable benefit: risk ratio for a given clinical context. For example, if a medicine is intended for chronic use then data about long-term safety as well as long-term effectiveness is ideally needed to inform this decision. This is especially pertinent with newly marketed medicines as the available evidence about safety at the time of marketing is limited, with a more complete profile emerging only after larger numbers of children have been exposed over a longer period of time.

Where alternative agents to treat a particular condition exist, routine use of a new medicine may only be justified if there is evidence from comparative studies showing an advantage in effectiveness and/or safety and/or cost-effectiveness in typical patterns of use in the relevant paediatric population. It is worth noting that any comparisons of safety data for newly marketed medicines versus older medicines will tend to be unfairly skewed in favour of the newer medicine by virtue of the more limited safety data available for new medicines.

The available data about effectiveness and safety should be weighed against the seriousness of the underlying condition. As a general rule, the less serious the health need, the higher the level of evidence needed to support use of the medicine. As previously discussed, this will need to be informed by expert judgments and the people and processes through which this is done will need to be given careful consideration.

Based on this assessment of the level and quality(42) of the scientific evidence available, the balance of benefits vs. risks, the seriousness of the health problem or magnitude of disease burden, and consideration of the availability of alternative treatments, an overall recommendation about off-label use could be presented in the following broad categories:

- *Recommend routine use*: if there is "high" or "moderate" quality of evidence and benefits clearly outweigh risks for a given health need in the paediatric population (i.e. "routine use justified");
- *Equivocal* (or reserve for "exceptional" uses): e.g. if there is "low" or "very low" quality evidence but benefits appear greater than risks based on available evidence in some circumstances. If this category of recommendation is used (e.g. serious or rare disease), it should be linked to rigorous outcome evaluation and regular review so that future practice could be better informed by new evidence. Depending on the health issue and context, this could be pursued either as part of a formal "research" study, or as part of approved "treatment" within a pre-specified clinical protocol that includes outcome evaluation. The potential biases introduced by the latter approach should be borne in mind when choosing between these options. This type of approach would be very similar to the "conditional approval" models currently being recommended for regulatory assessments of new medicines.(40, 60, 61)

- *Recommend against routine use:* e.g. if there is “low” or “very low” quality evidence with uncertain benefits and risks, or the available evidence demonstrates that overall risk:benefit ratio is (or would be) unfavourable in the relevant paediatric population.

These broad categorisations are suggested as a general guide, the specific details of which would benefit from further discussion. Some of these categorisations will involve value judgements (e.g. burden of disease, cost-effectiveness, availability of alternative treatments) that will differ between different countries and regions in the developed and developing world.

“Older” or off-patent medicines

In some instances, high quality research evidence supporting the use of a particular medicine (e.g. older off-patent medicines) may not be available and may be unlikely ever to become available. However, there may be extensive experience supporting the effectiveness and safety of such medicines. Although such data or “expert opinion” is considered to be of lower quality than high quality research evidence, there are examples where it may be used to inform decisions regarding off-label use of a medicine. There are several authoritative medicines’ compendia that make recommendations for appropriate use supported either by research evidence and/or consensus opinion based on extensive experience with various medicines (see section 5). These include the British National Formulary for Children, the Australian Medicines Handbook, and Therapeutic Guidelines (Australia). Other sources may include recommendations from professional societies, although the quality and validity of some of these can be quite variable. Less formal sources of “experience” or “opinion” based support are less acceptable, and caution is recommended when considering this level of support for off-label use.⁽⁶²⁾

This category of support for off-label use may be appropriate to consider for older medicines but is not recommended for newly marketed medicines, where the needed research should be done first (especially for medicines targeting diseases of high prevalence). It should be emphasised that this category of support for off-label use, even where it is used for justifying “established” uses, needs to be systematically and regularly reviewed as new research evidence becomes available. As previously discussed, some of the recent US initiatives have stimulated research on off-label uses of medicines in children, generating new evidence about efficacy, safety, and appropriate dosing, with significant implications for long-established prescribing practices.

Any use that may be recommended under this category should ideally be accompanied by a more systematic evaluation of outcomes (safety and effectiveness), especially in the longer term, if such evidence does not already exist. This type of data would then allow a regular re-assessment of the risk:benefit ratio of a particular medicine to either justify ongoing use or for discontinuation of the recommendation for that particular use. This type of approach would be particularly appropriate (and cost-effective) for certain medicines (e.g. high acquisition cost; high safety risk) or high-risk paediatric populations (e.g. younger age groups).

7. ISSUES FOR DISCUSSION:

- 1) Need to define the *people* and *processes* through which WHO will assess the appropriateness of applications for addition to the EML using the approach suggested in section 6. An appropriate mix of expertise is needed to ensure rigorous evidence review is conducted and carefully integrated with appropriate paediatric clinical expertise. This will be especially relevant when the quality of evidence is less clear and expert judgements will inform decisions about the validity of trade-offs between quality of evidence required vs. particular health needs and circumstances. Getting the “who” and the “how” right will be very important in ensuring the validity of WHO’s recommendations, helping meet essential child health needs globally while avoiding some of the unintended consequences detailed in section 4 of this paper.(63, 64)
 - Who should be these experts? (i.e. what are the specific areas of expertise needed? What is the appropriate mix of expertise, either in individuals or within any group charged with decision-making responsibilities?)
 - How should these experts be chosen?
 - By what process should these experts develop their final recommendations? The process for systematic evaluation of evidence is detailed above. However, given that in many instances evidence may be limited and opinions will need to be integrated into an overall recommendation, should there be a systematic process outlined for this element as well (e.g. formal consensus development methods)?
 - What type of conflict of interest (COI) policy is appropriate to apply in this circumstance? (e.g. public disclosure of potential COI only, or exclusion based on significant COI identified).(65) For example, some have suggested the exclusion of experts with financial ties to the pharmaceutical industry from expert groups providing advice to governments and drug regulators.(66)
- 2) Which drug regulatory bodies should be considered “competent” for the purposes of defining “approved” vs. “unapproved” uses at a global level;
- 3) Which medicines information resources should be considered “authoritative” for the purposes of defining “well accepted” off-label uses of older medicines at a global level;
- 4) Is the suggested system for grading and presentation of overall recommendations appropriate? Are there additional considerations that are relevant, especially from a developing world perspective?
- 5) How can any identified research needs generated by this process be linked into an effective global research agenda? How should these be prioritised and funded?
- 6) Which are the relevant groups to engage in a broader consultation process to assist in developing this discussion paper into a meaningful and useful global policy about off-label (or unlicensed) medicines use in the paediatric population?

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