Unlicensed and Off-label Drug Use in Children

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The purpose of licensing is to ensure that medicines are marketed only after having been examined for safety, efficacy, and quality.[1] When a drug is prescribed outside these parameters, this support is lacking. Despite this, unlicensed and off-label drug use in children is widespread.[2-23] This is ironic to say the least, since the licensing process itself was introduced in the US and European countries mainly as a response to drug-related tragedies [chloramphenicol-induced gray baby syndrome, thalidomide-induced phocomelia and deaths following diethylene glycol poisoning] that occurred in newborn babies, infants and children. Estimated to vary from 10-72% (Table 1), the magnitude of such use varies amongst others, according to the level of healthcare available, subspecialty concerned and certain patient characteristics. The prevalence of off-label and unlicensed drug use is higher in neonates and infants and in premature and low birth-weight babies.[21] Topical preparations such as eye drops, ear drops and dermatological products also account for much of the off-label and unlicensed drug use,[2,21] as these are hardly ever subjected to formal evaluation in children. Amongst the systemic drugs, bronchodilators, anti-migraine prepa-

Why is Unlicensed and Off-Label Drug Use Common?

Off label drug use refers to the use of drugs outside the conditions of the product license in terms of dose, patient age, route of administration, indication and contra-indication;[2] while unlicensed use refers to using a drug in children when it has not received market authorization for use in them. For several years, children have been excluded from clinical trials carried out during the process of market authorization; as the society and law makers thought it prudent not to expose children to molecules, whose safety and efficacy had not been established. This resulted in drugs being marketed without pediatric safety and efficacy data. Ironically, society’s desire to protect children from clinical studies has resulted in a much larger number of children getting exposed to the drugs when a clear evidence of safety, efficacy or favorable risk-benefit ratio has not been generated, when information about effective and safe dosages are not available and when there is no active monitoring for adverse events and that too, in an uncontrolled fashion. Also, such exposure in clinical practice does not yield significant generalizable data, as practitioners do not report off-label or unlicensed drug use. It is not surprising that now the fundamental dilemma of whether children are to be protected

Table 1: Summary of selected studies estimating the use of drugs beyond license

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Clinical setting (Country)</th>
<th>No of prescriptions (No. of patients)</th>
<th>Unlicensed or off-label drug use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner, et al., 1996[2]</td>
<td>1 PICU (UK)</td>
<td>862 (166)</td>
<td>31</td>
</tr>
<tr>
<td>Conroy, et al., 1999[4]</td>
<td>1 NICU (UK)</td>
<td>455 (70)</td>
<td>64.6</td>
</tr>
<tr>
<td>Conroy, et al., 2000[8]</td>
<td>5 pediatric wards (five European countries)</td>
<td>2262 (624)</td>
<td>46</td>
</tr>
<tr>
<td>Chalumeau, et al., 2000[10]</td>
<td>77 pediatricians (France)</td>
<td>2522 (989)</td>
<td>33</td>
</tr>
<tr>
<td>Craig, et al., 2001[12]</td>
<td>1 pediatric unit (Northern Ireland)</td>
<td>237 (74)</td>
<td>22.8</td>
</tr>
<tr>
<td>Pandolfini, et al., 2002[14]</td>
<td>9 pediatric wards (Italy)</td>
<td>4625 (1461)</td>
<td>60</td>
</tr>
<tr>
<td>‘t Jong, et al., 2002[16]</td>
<td>Community† (The Netherlands)</td>
<td>17453 (6141)</td>
<td>28.9</td>
</tr>
<tr>
<td>Bucheler, et al., 2002[17]</td>
<td>Records with health insurer† (Germany)</td>
<td>1.74 million</td>
<td>13.2</td>
</tr>
<tr>
<td>Carvalho, et al., 2003[18]</td>
<td>PICU(Brazil)</td>
<td>747 (51)</td>
<td>54.2</td>
</tr>
<tr>
<td>Schirm, et al., 2003[19]</td>
<td>Community† (The Netherlands)</td>
<td>66222 (18943)</td>
<td>37.2</td>
</tr>
<tr>
<td>Neubert, et al., 2004[20]</td>
<td>Pediatric isolation ward (Germany)</td>
<td>740 (178)</td>
<td>22.7</td>
</tr>
</tbody>
</table>

*retrospective studies; †: Presentation monitoring studies; NA: not available
from drug studies, or is it important to evaluate drugs adequately in children before they are used in pediatric practice, is being resolved in favor of the latter. Historically, the pharmaceutical industry has been less enthusiastic in conducting clinical trials in children as they are costlier and logistically more challenging to undertake. The fact that the pediatric market-share is miniscule as compared to the adult market also acts as a dampener.

Non-availability of pediatric formulations is a common reason for unlicensed drug use. Young children require liquid preparations and dispersible tablets. For many molecules, such preparations are not available. Hence, extemporaneous dispensing in the form of crushing tablets or opening capsules and suspending contents is resorted to so as to produce a liquid preparation that a child can take.

**Associated Risks**

Given the fact that over 70% of all Physicians’ Desk Reference (PDR) entries do not have adequate pediatric labeling, off-label and unlicensed drug use becomes a necessity. However, such use is not without its risks. When extemporaneous dispensing is resorted to, there is little information regarding the drug’s bio-availability and stability. It is possible that the child might receive an unstable and hence an ineffective drug. The medium used to dissolve the drug powder, if inappropriate, could cause adverse reactions. When pediatric dose has not been established, doctors calculate pediatric dose on the basis of adult dose. This could be hazardous as children are not just miniature adults. Their body composition changes over the years and so does their drug-metabolizing capability. The practice could result in children receiving sub-optimal or excessive doses. Even use of unlicensed topical preparations could result in unexpected events. For example, given their greater surface area as compared to body mass, relatively larger amounts of topically applied dermatological preparations could get absorbed systemically. It should be borne in mind that some studies do indicate that the frequency of adverse drug reactions is higher with unlicensed and off-label drug use. In some countries, insurance companies do not reimburse expenses incurred on off-label and unlicensed drugs, putting families at a financial disadvantage.

**Concerns for the Treating Doctor**

It is true that the terms ‘unlicensed’ do not imply disapproval or that the practice is improper. They only imply that pharmaceutical companies have not performed clinical trials and, therefore, evidence of tolerability and efficacy is not available to satisfy licensing authorities. Such data may not be really available or the concerned pharmaceutical company may not be interested in submitting this data for improving pediatric labeling. Whatever be the reason, when a drug is used outside the limits of its label, neither the company nor the authorities take any legal or ethical responsibility for the occurrence of an unexpected event. It may still be proper and lawful for a doctor to prescribe an off label drug, but the responsibility lies entirely with the prescriber. In addition, the doctor has to spend more time with parents explaining to them why a drug does not have adequate pediatric labeling. On the other hand, a doctor deciding to prescribe drugs only as per label would find his therapeutic armamentarium greatly curtailed. And such an approach besides being impractical, is untenable. It is not ethical for a doctor to withhold using a potentially useful drug in a patient, just because it would amount to off-label use.

This puts doctors caring for children in an unenviable situation. Given the large number of drugs without adequate pediatric labeling, they are frequently called upon to use their judgment regarding the use of these drugs. It is expected that the decision to use the drug and its dose be based on evidence and authoritative professional opinions. But in reality, the licensing authorities do not seem to have enough evidence about the drug’s efficacy, safety and risk-benefit ratio, the label on the drug does not indicate a particular dose, the scientific information available from medical literature is confusing at best and there is hardly any single authoritative source of reference available. The doctors fear that they could be sued for malpractice for indulging in off-label drug use should an unexpected event occur. It needs to be emphasized that the doctor could justify such use, provided the decision is based on what is good medicine and what is best for the patient regardless of conforming to labeling. In a liability suit, drug labeling may have evidentiary weight, but it, per se, is not intended to set a standard for good medical practice. In fact, a doctor could be subjected to claims of malpractice if a patient is denied the best potential treatment just because it was unlicensed or off-label.

**Remedial Actions and Future**

Although, statements from professional bodies highlight that unlicensed and off-label drug use is a vital part of children’s drug therapy and that this practice should use the best information available and should be justifiable as being in accordance with a respectable, responsible body of professional opinion; it is not a desirable state. Complacency about the lack of evidence-based information on drugs for the children is unacceptable, as the practice does expose children to drugs whose efficacy, safety and risk-benefit ratio are not known and puts undue stress on the treating doctors. As pointed out by Boos, a widespread off-label use of drugs makes mockery of licensing and its declaration of bankruptcy. In this situation, the label is off use in that it leads to a general tendency to ignore the package inserts and the guardians not finding any relevant information in the package. More important offshoots of this kind of practice will be that the physicians having to take on more legal responsibility, the authorities not being able to control the market and the companies not knowing what happens with their drugs.

The society, the lawmakers and the pharmaceutical industry need change their attitudes and mindset and should understand and acknowledge that children have as much right to effective, safe and quality drugs as adults. To ensure that this fundamental right to safe therapy is protected, we need to act...
through two pathways. One is through steps intended to generate more pediatric data on safety and efficacy of drugs through pediatric clinical trials and the second by making efforts intended to make off-label safer.

Several innovative steps have been taken in the western countries to coax, entice, stimulate and even compel the pharmaceutical companies to undertake clinical trials in children. Having failed to elicit the desired effect by asking the drug companies to provide pediatric indications and dosage in the label based on evidence derived from adequate and well-controlled studies in the pediatric population, the FDA came out with the voluntary pediatric exclusivity (PE) clause within the FDA modernization Act (FDAMA) 1997. It provided exclusive rights to the company to market a drug for an extended period of six months, if the company made a fair attempt to generate pediatric data regarding the drug by undertaking pediatric clinical trials. The approach was innovative: the FDA acknowledged that undertaking pediatric clinical trials put financial burden on companies and hence attempted to provide compensation / fiduciary incentive. The limitations included its voluntary nature and its ineffectiveness with regard to off-patent drugs. Through Pediatric Rule (PR) that came into effect in 1999, the FDA moved forward by mandating manufacturers to submit safety and effectiveness data on relevant pediatric age groups before approval. The PR applied to biologics as well and could be applied multiple times during the life cycle of a drug. The two measures (PE and PR) were successful with FDA getting several requests for conducting pediatric clinical trials. The Best Pharmaceuticals for Children Act (BPCA) established an office of pediatric therapeutics and created a Foundation of National Institutes of Health (NIH), which would generate funds for the study of drugs (including important off-patent drugs), in children. The Pediatric Research Equity Act (PREA) re-established the FDA's authority to mandate pediatric drug development and made a pediatric assessment mandatory at the pre-IND meeting with FDA. The European countries have also taken steps to ensure that pediatric studies are conducted more often. Prioritizing building infrastructure for such studies, they have concentrated on developing network of pediatric clinical investigator and providing training in pediatric clinical pharmacology. Having seen the failure of “European guidance on clinical investigation of medicinal products in children” in stimulating pharmaceutical industry to improve pediatric labeling scenario, the European Union Council has published a consultation document “Better medicines for Children” which it is hoped would result in legislation to improve the situation.

Compelling and motivating companies to undertake pediatric clinical trials is not the whole answer to the issue. There is a need identify and address factors that make the conduct of pediatric clinical trials difficult. The factors responsible include those related to difficulties in recruitments, obtaining ethical clearance and having sensitive and trained investigators. These could be tackled by providing community education regarding need for undertaking clinical trials in children, providing risk categorization guidelines to Institutional Review Boards (IRB), training and sensitizing members of the IRB regarding risk assessment and scientific issues related to children’s rights as participants and providing training to investigators. The FDA has provided broad guidelines regarding factors to be considered (degree of risk involved, possibility of direct benefit to the participant and prospect of generating vital generalizable knowledge) while providing ethical clearance. But these need not to be made more precise. The importance of conducting these studies with greatest degree of professionalism, while adhering to the highest level of ethical standards cannot be over-emphasized. Any slacking in this regard could lead to public outcry that would set the clock of readiness for conducting trials back by decades. Therefore, the IRB will have to become more pro-active and assume their monitoring role with greater alacrity. Boos in a thought-provoking editorial has pointed out that testing indication by indication and age group as pre-condition for labeling cannot work in rare diseases and the expectation to supply standard data sets with hundreds of patients is difficult to attain in severe or rare pediatric illnesses. In these circumstances, conducting studies with lower level of significance or lower power would be worth thinking about; but is likely to invite opposition since nobody wants to systematically reduce the standards for specific patient groups. Although, randomized controlled interventional trials have been the standard design used for determining efficacy and safety; under special circumstances, we should determine if we could use alternative (epidemiology and prospective observational cohort) designs for generating vital efficacy and safety data.

If we intend to rid of the off-label use, we will have to indulge in, “out of box” thinking and devise novel approaches. At the moment, only the concerned pharmaceutical company can initiate the process of label change. But given the economic considerations, why should a company be interested initiating this costly process, if the drug is being used any way and is off-patent? To counter this phenomenon, legal provisions should be enacted that would require pharmaceutical companies to summarize published data, medical guidelines and other clinical experience with respects to their drug product and submit this information to the authorities, who could eventually legalize the broad off-label therapeutic experience, whenever possible. Secondly, newer legal provisions should allow pediatric and medical societies to review available evidence and initiate label changes. These societies should also encourage its members, who choose to prescribe a medication with no or limited pediatric data to document and publish experiences from such off-label use. In fact, the societies could also maintain registries for certain critically important drugs, where pediatric data needs to be generated.

We should assess the effectiveness of the measures undertaken to stimulate pediatric trials. However, given the backlog of drugs that do not have pediatric labeling, inherent problems in conducting pediatric studies and limitations of various initiatives, it is possible that off-label and unlicensed drug use in children would continue for several years. Hence, we should also try and implement measures that would make such use as safe as possible. Updated information regarding drugs of interest should be provided to assist doctors take informed decisions.
regarding off-label drug use. Although medical literature does not offer this information; a newsletter dedicated to publishing such specific data regarding drugs likely to be used for off-label indications would be of great use to doctors. The pharmacopoeias should improve pediatric coverage[25] and WHO and UNICEF should develop a pediatric-specific essential medicine list. This would help to increase the awareness of the need for pediatric specific medications and highlight areas of priority where medications or formulations are lacking.[34]

The pediatric societies should provide evidence-based guidelines for appropriate drug choice and use in pediatrics on the lines of Medicines for children produced by Royal College of Pediatrics and Child Health. These would reflect the expert professional opinions that doctors can depend upon. In addition, drug information services provided by pharmaceutical companies and clinical pharmacology units of academic instructions should be optimized. Guidelines for preparation of extemporaneous formulations, when no licensed preparations exist need to be generated and disseminated to ensure that children continue to receive safe medications in a suitable form.

The situation in the developing countries needs to be studied, as, barring a few, all the studies on this issue have been carried out in European countries, US and Australia. This noteworthy absence of studies from developing countries could be indicative of lack of awareness or interest amongst health care professionals. Either way, this is a worrisome phenomenon. If doctors in the developing world are not aware of or are not sensitive to the issue of unlicensed and off-label drug use in children, they are likely to prescribe these drugs even when a proven, safe and effective option is available, thereby exposing children in these countries to unproven therapies. The consequences could be graver with lesser awareness amongst the general public and the medical profession and ineffective implementation of inadequate legislation. Just one example would be sufficient to emphasize that different and more steps would be required to tackle the issue: in most advanced countries, detail men employed by the pharmaceutical industry are prohibited from briefing doctors about off-label use. However, in developing countries these detail men routinely inform medical practitioners about off-label indications, without categorizing them as “off-label” (personal experience).

Although, it is heartening to note that the issue of off-label and unlicensed drug is receiving attention from several quarters and that some well-intended steps are being taken, a lot more remains to be done. Every segment concerned with and about the health of the children like the government, the legislative bodies, the regulatory authorities, the consumer organizations, the medical practitioners, the pharmaceutical industry and the academic institutions will have to work in tandem and in collaboration to ensure that children receive effective, safe and quality drugs which is their birthright.

References

31. Bavdekar SB. Protecting children participating in Research trials: Review Boards should take up Pro-active Role. Indian Pediatrics [in press].