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# Defining off-label and unlicensed use of medicines for children: Results of a Delphi survey

Antje Neubert[a,1], Ian C.K. Wong[a,1], Alessandro Bonifazi[b,1], Mariana Catapano[b,1], Mariagrazia Felisi[b,1], Paola Baiardi[b,1], Carlo Giaquinto[c,1], Catherijne A.J. Knibbe[d,e,1], Miriam C.J.M. Sturkenboom[f,1], Maisoon A. Ghaleb[g,1], Adriana Ceci[b,*,1]

[a] *Centre for Paediatric Pharmacy Research, The School of Pharmacy, University of London and Institute of Child Health, University College London, London, United Kingdom*
[b] *Consorzio per Valutazioni Biologiche e Farmacologiche, Pavia, Italy*
[c] *Department of Paediatrics, University Hospital Padova, Italy*
[d] *Leiden/Amsterdam Center for Drug Research, Division of Pharmacology, Leiden University, Leiden, The Netherlands*
[e] *Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands*
[f] *Pharmacoepidemiology Unit, Departments of Medical Informatics and Epidemiology & Biostatistics, Erasmus University Medical Center, Rotterdam, The Netherlands*
[g] *Department of Practice and Policy, The School of Pharmacy, University of London, United Kingdom*

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ABSTRACT

The aim of this Delphi survey is to develop common definitions for unlicensed and off-label drug use in children to be used for research and regulatory purposes.

After a literature review on the current status of unlicensed/off-label definitions, a two-stage, web-based Delphi survey was conducted among experts in Europe. Their opinion on concerns, rules and scenarios regarding the unlicensed and off-label use of medicines were obtained. Results were then consulted with the European Medicines Agency (EMEA) before the final proposal was circulated to participants.

Eighty-four experts were invited to participate (scientists, health professionals, pharmaceutical companies, regulatory agencies), 34 responded to the first round questionnaire and participated in subsequent rounds. Consensus was reached for the majority of questions. The lowest level of consensus reached was for questions related to a different formulation or if a drug was given although contraindicated. At the final step, 85% of the responding experts agreed on the proposed definition for off-label (use of a drug already covered by a Marketing Authorisation, in an unapproved way) and 80% on the definition for unlicensed (use of a drug not covered by a Marketing Authorisation as medicinal for human use), respectively.

Results will facilitate the conduct of pharmacoepidemiological studies and allow comparison between different countries. The Delphi panel agreed that the definitions should be circulated within the scientific community and recommended to be adopted by relevant regulatory authorities.



## 1. Introduction

Medicines are frequently prescribed to children without being approved for the paediatric population [1–5]. Although the use of 'off-label' and 'unlicensed' drugs in children is widespread in Europe and worldwide, there is no common scientific and regulatory approach to this phenomenon and, in particular, a shared definition is missing [6].

According to Article 42 and 43 of the European Paediatric Regulation [7], data available on existing use of medicinal products will have to be collected and shared among Member States of the European Union in the near future. Based on this information, an inventory of therapeutic needs will be established by the European regulatory body. The lack of a common definition makes comparison between different countries difficult [7,8].

Furthermore, a common definition will facilitate rigorous pharmacoepidemiological studies, encouraging the adoption of a common European policy addressing 'off-label and unlicensed use' in the paediatric population.

The aim of this Delphi survey was to obtain consensus on common definitions for unlicensed and off-label use of medicines

* Corresponding author. Tel.: +39 0382 25075; fax: +39 0382 536544.
*E-mail address:* aceci@cvbf.net (A. Ceci).
[1] On behalf of the TEDDY Network of Excellence.

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**Table 1**
Composition of the expert panel.

| | Invited, % (*n*) | First round, % (*n*) | Second round, % (*n*) | Third round,[a] % (*n*) |
|---|---|---|---|---|
| Health professionals | 14.3 (12) | 20.6 (7) | 21.7 (5) | 25.0 (5) |
| Industry | 8.3 (7) | 8.8 (3) | 13.0 (3) | 10.0 (2) |
| Regulatory | 20.2 (17) | 14.7 (5) | 8.7 (2) | 20.0 (4) |
| Scientists | 52.4 (44) | 55.9 (19) | 56.5 (13) | 45.0 (9) |
| Other | 4.8 (4) | 0 | 0 | 0 |
| Total | 100 (84) | 100 (34) | 100 (23) | 100 (20) |

[a] The third questionnaire was applied to obtain agreement on the definition from the experts.

in children in order to improve the use of the European official regulatory terminology and facilitate pharmacoepidemiological research.

## 2. Materials and methods

### 2.1. Literature review

In designing the first questionnaire, previous definitions for "unlicensed" and "off-label" drug use were identified. A systematic literature review was conducted with a PubMed search of documents published from 1995 to 2005, containing the following combination of words: "children, prescriptions, unlicensed, off-label" (limits: under 18 years).

Following screening, the relevant papers providing useful definitions were further investigated; similarities and differences among the sources were evaluated.

### 2.2. Questionnaire

Based on the results of the literature review, a Delphi survey (questionnaire) was designed and conducted using a web-based application [9,10]. The Delphi is a group facilitation technique that seeks to obtain consensus on the opinion of "experts" through a

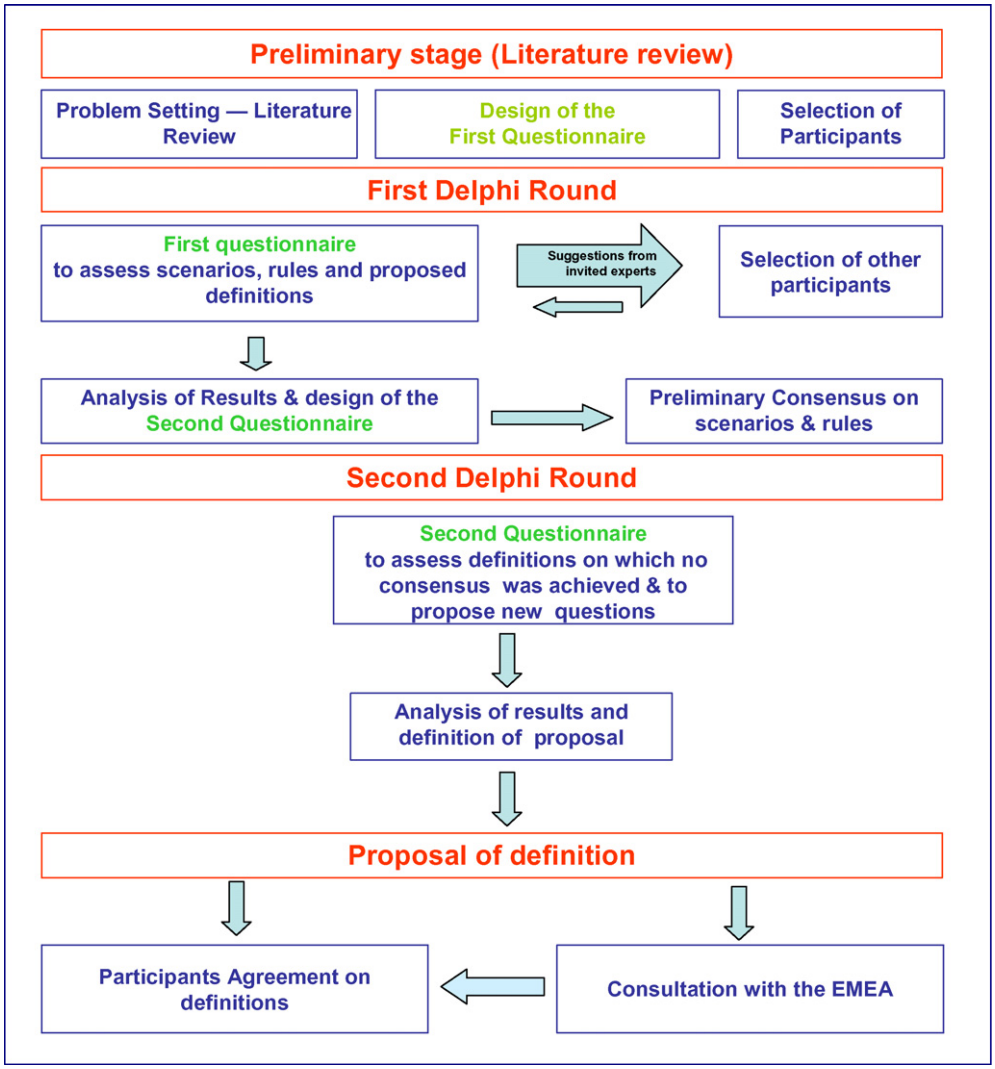


**Fig. 1.** Schematic description of the survey.

**Table 2**
Questions applied in the first and second round of survey including consensus level.

| Questions | Consensus level first round, % (*n*) | Consensus level second round, % (*n*) |
|---|---|---|
| PROCESS (P) | | |
| P.1.1. A unique definition of the 'off-label' and 'unlicensed' terms at the European level could be useful for professionals, Health Authorities and Pharmaceuticals firms involved in paediatrics | ≈95% (32) | |
| P.1.2. An internationally agreed definition of 'off-label' and 'unlicensed' use is needed at the ICH (International Conference on Harmonisation) level | ≈90% (30) | |
| P.1.3. The following groups and organizations should be involved in the development of a definition for unlicensed and off-label uses at the European level | | |
| European Regulatory Authorities | ≈80% (28) | |
| Healthcare specialists (biomedical, nursing and pharmacists) | ≈65% (22) | |
| Pharmaceutical companies | ≈55% (18) | |
| Regulatory agencies | ≈75% (26) | |
| Academics and scientists | ≈60% (21) | |
| Experts in legal, ethical, social and economic issues in the pharmaceuticals field | ≈55% (18) | |
| P.1.4. The following groups and organizations should anyway be consulted during the development of unlicensed and off-label use definitions at the European level | | |
| European Regulatory Authorities | ≈60% (21) | |
| Healthcare specialists (biomedical, nursing and pharmacists) | ≈60% (21) | |
| Pharmaceutical companies | ≈75% (25) | |
| Regulatory agencies | ≈55 % (19) | |
| Academics and scientists | ≈55 % (18) | |
| CONCERNS (C) | | |
| C.1.1., C.1.2., C.2.1. The major causes of concern about the 'off-label' use in the paediatric population are | | |
| Children safety | ≈99 % (33) | |
| Ethical aspects | ≈55% (18) | |
| Lack of efficacy | | ≈90 % (22) |
| C.1.3. The major causes of concern about the 'unlicensed' use in the paediatric population are | | |
| Children safety | ≈85% (29) | |
| Ethical aspects | ≈50% (17) | |
| Legal aspects | ≈50% (17) | |
| SCENARIOS (S) | | |
| S.1.1. The use of an authorised drug outside the terms of the existing Marketing Authorisation is to be considered off-label | ≈90% (31) | |
| S.1.2. The use of an authorised drug through an unapproved formulation is to be considered | | |
| Off-label | 41% (14) | |
| Unlicensed | 47% (16) | |
| S.2.1. The use of an authorised drug through an unapproved route of administration should be considered equivalent to the use of an unapproved formulation | | 54% (13) |
| S.2.2. The use of an authorised drug in an unapproved formulation that is not prepared under GMP conditions (e.g. by parents) should be considered | | |
| Unlicensed | | 50% (12) |
| Off-label | | 25% (6) |
| Neither | | 26% (6) |
| S.2.3. The use of an authorised drug in an unapproved formulation that is prepared under GMP conditions (e.g. by pharmacists) should be considered | | |
| Unlicensed | | 42% (10) |
| Off-label | | 42% (10) |
| Neither | | 17% (4) |
| S.1.3. The use of an authorised drug through an unapproved administration route is to be considered | | |
| Off-label | ≈70% (23) | |
| S.1.4. The use of an authorised drug in an unapproved dosage is to be considered off-label | ≈80% (28) | |
| S.1.5. The use of an authorised drug in a condition labeled as "contraindicated" or "not indicated" is to be considered off-label | 59% (20) | |
| S.2.4. The use of an authorised drug in a condition labeled as "not indicated" is to be considered off-label | | 70% (17) |
| S.2.5. The use of an authorised drug in a condition labeled as "contraindicated" enters greater legal implications than the use in a condition that is not indicated | | 90% (21) |
| S.2.6. The use of an authorised drug in a condition labeled as "contraindicated" should be considered as | | |
| Off-label | | 21% (5) |
| Unlicensed | | 33% (8) |
| Neither | | 46% (11) |

Table 2 (*Continued*)

| Questions | Consensus level first round, % (*n*) | Consensus level second round, % (*n*) |
|---|---|---|
| S.1.6. The use of an authorised drug in a different and unapproved age group is to be considered off-label | ≈80% (27) | |
| S.1.7. The use of an authorised drug in an unapproved indication is to be considered off-label | ≈75% (25) | |
| S.1.8. The use of a drug that has never been authorised by any European Authority (neither for adults nor for children) is to be considered unlicensed | ≈80% (27) | |
| S.1.9. The use of chemicals and other active substances licensed as chemical, biological, nutritional, herbal products and used with the aim of preventing, diagnosing or curing an human disease is to be considered | | |
| Unlicensed | ≈71% (24) | |
| S.1.10. The sustained use of experimental drugs after the end of trials but before they are granted a Marketing Authorisation, is to be considered unlicensed | ≈73% (25) | |
| RULES (R) | | |
| R.1.1. The off-label use should be allowed to prescribers only under specific conditions | ≈70% (24) | |
| R.1.3. The off-label use of OTCs should not be allowed to patients and parents | ≈65% (22) | |
| R.1.4. Marketing Authorisation Holders should not be allowed to promote off-label use | ≈80% (28) | |
| R.1.5. The use of a drug that is not yet licensed in the patient's country while it is licensed in other European countries should be allowed to prescribers under specific conditions | ≈65% (22) | |
| R.1.6. The use of an 'experimental drug' that is not yet licensed in Europe while it is licensed in other ICH countries should be allowed to prescribers under specific conditions | ≈70% (24) | |
| R.2.1. Specific definitions for the off-label use should be developed for paediatric populations, rather than adopting common definitions for all age groups | | 60% (14) |

series of structured questionnaires. It is an iterative multistage process designed to combine opinion into group consensus [11,12]. This flexible approach is commonly used within the health and social sciences. Two on-line questionnaires were administered iteratively in order to build the consensus by moving from concerns, scenarios and rules towards shared definitions. Scenarios and rules represented the building blocks for the development of definitions.

Consensus was defined as a qualified majority of 2/3 (66.7%) in all responses.

Preliminary results were submitted to the European Medicines Agency (EMEA) to incorporate their comments into the final conclusions of the survey.

The questionnaire consisted of five sets of questions, comprising:

- the need and conditions for the development of common definitions (i.e. the process);
- the concerns arising from off-label and unlicensed use of medicines in children;
- a set of scenarios to distinguish off-label from unlicensed use;
- tentative rules to regulate each use;
- proposed definitions.

A pilot round was tested with five partners of the TEDDY Network [13]; the questionnaire was then modified according to the comments of the partners.

### 2.3. Participants—expert panel selection

For this Delphi survey, experts were approached on the basis of their recognised experience in the field [9]. Experts included had the following backgrounds:

- Scientists (i.e. academia, researchers, existing research networks and groups, scientific societies), such as clinicians, pharmacologists and methodologists.
- Health professionals (i.e. medical doctors, pharmacists, ethical bodies and other care givers).
- Industry (Small and Medium Enterprises (SME) and larger companies).
- Regulatory agencies (at European and national level).

Invited participants either appeared on PubMed as authors of publications on off-label and unlicensed use definitions or were contacts of the authors with recognised expertise in the field of paediatrics. Of 84 invited experts, 34 (40%) agreed to participate and answered the first round of questions (Table 1).

### 2.4. The Delphi process

Given the context of this study, non-quantitative, forced-choice, response scales were chosen. In the first round, participants were invited to express their opinions on sets of questions, as well as to suggest tentative definitions for off-label and unlicensed use. A second round was set up to resubmit questions for which a qualified majority (>2/3 of responses or more) could not be reached.

After the second round, a proposal for definitions was arrived at and the results were presented to an ad hoc meeting of the Paediatric Working Party (PEG) at the EMEA for consultation.

The results of the second round of Delphi and a final proposal on definitions was then circulated to the experts for the final feedback in order to confirm the agreement of the finally proposed definition.

A schematic diagram summarizing the Delphi process is shown in Fig. 1.

## 3. Results

### 3.1. Literature review

The literature search revealed a total of 66 publications relating to off-label or unlicensed drug use in children between 1995 and 2005. Screening of these references revealed that 14 of these provided definitions for both off-label and unlicensed drug use [14–27]. Five additional publications dealt with off-label use only and did not distinguish between the two categories [28–32].

Review of the definitions showed many similarities but also crucial differences. For instance, some authors [19,27] consider that if

no dosage for the particular age group is given in the product information, the use is unlicensed. However, other studies judge the use of a drug outside the dosage information in the product information as off-label.

One study [15] considers only the use of medicines which do not have any license in adults or children as unlicensed and the use of a medicine outside its product license as off-label.

Some authors judge extemporaneous formulations [20] or formulations manufactured under a special license as unlicensed [16] and a formulation that is not approved for children or has been modified as off-label. Other authors consider any modified or special formulations both as unlicensed [25] and off-label [29,30].

### 3.2. Survey results

#### 3.2.1. First Delphi round

As shown in Table 2, consensus was reached in the majority of questions within the first round. Eight of the 10 scenarios had a consensus level above 2/3. However, consensus was not reached for the following:

The use of an authorised drug in an unapproved formulation made by pharmacists, paediatricians or patients was judged either 'off-label' (41.2%) or 'unlicensed' (47.1%). However, some respondents (12%) have underlined that 'unapproved formulation and unapproved route of administration should be considered in the same category'. The rationale behind this was that the lack of "Good Manufacturing Practice" (GMP) in both situations could affect relevant pharmacological characteristics of a medicinal product.

The use of an authorised drug in a condition labelled as 'contraindicated' or 'not indicated' has been considered either off-label (58.8%) or unlicensed (26.5%). Some respondents (6%) have also suggested such use to be 'malpractice'.

#### 3.2.2. Second Delphi round

In the second round, a total of 12 questions were applied with the majority focusing on the 2 scenarios for which no consensus was reached in the first round (Table 2). Use of an unapproved formulation (even in the case when GMP is applied by an experienced pharmacist and use of a drug in a 'contraindicated' condition are considered with criticism and a consensus definition was not reached (Table 2).

### 3.3. Agreed definitions by the Delphi panel

Taking into consideration the consensus levels of the survey, and the consultation with the EMEA, the following definitions were finally proposed:

"Off-label use" means 'all uses of a marketed drug not detailed in the SPC including therapeutic indication, use in age-subsets, appropriate strength (dosage), pharmaceutical form and route of administration'.

"Paediatric off-label use" specifically includes: 'all paediatric uses of a marketed drug not detailed in the SPC with particular reference to:

- therapeutic indication
- therapeutic indication for use in subsets
- appropriate strength (dosage by age)
- pharmaceutical form
- route of administration'

"Unlicensed use" means 'all uses of a drug which has never received a European Marketing Authorisation as medicinal for human use in either adults or children'.

The agreement from the experts on the finally proposed definitions for off-label and unlicensed use was 85% and 80%, respectively.

### 3.4. Consultation with the EMEA Paediatric Working Party (PEG)

The results of the survey were presented to the EMEA Paediatric Working Party (PEG) in March 2007. Following this meeting, a letter was received clarifying EMEA opinions, related below [33]:

1. The need for a definition is recognised at regulatory level and such a definition will be provided in the European Glossary. An agreement at the International Conference of Harmonisation (ICH) level is not considered necessary.
2. Within the EU pharmaceutical legislation, the use of a drug that has been granted a European Marketing Authorisation (MA) cannot be defined unlicensed, but 'off-label' at most.
3. Use of a drug that has never been granted a European Marketing Authorisation has to be defined as unlicensed.
4. The use of drugs 'contraindicated' for children is 'off-label'. In this regard the Agency underlined that a contraindication listed in the summary of product characteristics (SPC) and patient leaflet (PL) should be exclusively reserved for cases where there is clear evidence that the product should not be used in children.

All the above issues were then considered in the final definitions.

## 4. Discussion

This survey confirmed the need for a common definition for unlicensed and off-label uses which should be incorporated into European legislation.

The need for a common definition is mainly derived from the fact that, while many previously published studies [1–4,34] commonly refer to off-label as the use of drugs outside the terms of an 'approved label' and 'official documents', other characteristics such as applying a dosage not given in the summary product characteristics (SPC) or patient leaflet (PL) use of a drug in a contraindicated condition, application of a drug via a different route of administration or within a different formulation are sometimes considered as off-label and sometimes considered as unlicensed.

With regard to the use of authorised drugs in a 'contraindicated' or 'not indicated' condition, it was noted that definitions are often influenced by concerns on the legal implications of such use (often perceived as 'malpractice'). However the principal concerns expressed regarding the use in an unapproved "route of administration" or in an "extemporaneous formulation" were; that 'the manipulation of the drug as well as the lack of information on the acquired physicochemical properties could affect relevant pharmacological characteristics'. For these reasons, previously these uses have often been considered 'unlicensed'.

Such controversies are still present in recently published contributions where a remaining heterogeneity of the definitions applied is evident (Table 3) [1,2,36,38–41].

Our survey has mainly resolved these controversies. Accounting for the regulatory point of view, it was agreed that uses referring to 'marketed drugs', i.e. drugs which have a Marketing Authorisation will be considered 'off-label' whereas those referring to 'unmarketed drugs', i.e. drugs without Marketing Authorisation are to be considered 'unlicensed'.

We also highlighted other concerns arising from off-label/unlicensed use, which may require a 'case by case' approach. For example, the use of drugs in an unapproved dosage may lead to a poor risk/benefit ratio if the dosage was extrapolated from adults or from a different age category. Additionally, any manipulation of drugs such as the preparation of extemporaneous formulation

**Table 3**
Recent Controversies in the definition of "off-label" and "unlicensed" uses.

| Year | Authors and reference | Definition | |
|---|---|---|---|
| | | Off-label | Unlicensed |
| 2008 | Hsien et al. [39] | Off-label use was defined due to age, indication, route of application and dose | Not done |
| 2007 | Yoon et al. [40] | Off-label (was) based on minimum age criteria | Not done |
| 2007 | Volkers et al. [41] | Clinically accepted off-label indications | Some drugs are defined 'unlicensed' for age |
| 2007 | Dell'Aera et al. [1] | Licensed drugs used in children in lack of information for paediatric use in MA or licensed for paediatric use, but used off-label with regard to age, dose, route of administration and duration of treatment | Unlicensed drugs<br>Personalised galenic preparations<br>Drugs used as special formulations<br>Drugs used for many years, but without any product license |
| 2007 | Shah et al. [2] | Off-label drug use referred to the age categories approved by FDA | Not done |
| 2007 | McCowan et al. [42] | A formulation not licensed for use in children, not licensed for use in a particular age group, or with a specific dose not licensed for use | Not done |

or the use of an unapproved route of administration may increase their toxicity [35].

For the first time, a definition is proposed for the 'unlicensed' and 'off-label' use of medicines specifically targeted for the paediatric population as agreed by a panel of European experts in this field. Considering the 40% initial response, there was a fair distribution of experts with different backgrounds (Table 1), ensuring the integration of all viewpoints.

These results should be circulated to all interested parties to enlarge consensus within the scientific community and promote the correct use of terminology. Furthermore, competent authorities should be recommended to include these definitions in the EU glossary, as envisaged by the EMEA.

Undoubtedly, the definitions for the off-label/unlicensed use of drugs with particular reference to the paediatric age will facilitate a common understanding of their terms of reference. It should be noted that important aspects, such as extemporaneous use or permission schemes to allow controlled off-label and unlicensed uses of drugs are not entirely resolved yet (Table 2). These issues will require further work particularly involving the scientific community.

Through the consultation with the EMEA we have had the opportunity to both confirm our findings on the proposed definitions and to underline the aspects for which further clarifications and consensus are needed among scientists and between experts and regulatory stakeholders.

In particular, while the consultation enabled us to provide a widely acceptable definition on the off-label and unlicensed terms, the EMEA has rejected the proposal (agreed by 90% of panellists) to extend such definition at an international level (i.e. ICH—International Conference on Harmonisation). On this point the EMEA opinion was that there is no need to do so from the regulatory point of view, but it is possible on the scientific one.

Finally, another important aspect underlined by the results of the survey is the need to keep unlicensed and off-label drug prescriptions limited to well-defined cases rather than making it common practice. However, the solution envisaged in our survey results (e.g. permission schemes to allow the use of 'off-label' drugs for which a well established current practice is known) is not recommended by the Agency, because it seems to be in contrast with the aims of the Paediatric Regulation, that is focused on providing tested and licensed medicines to children [37].

All these issues will require further work, particularly involving the scientific community in a common effort with the regulatory authority.

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## References

[1] Dell'Aera M, Gasbarro AR, Padovano M, Laforgia N, Capodiferro D, Solarino B, et al. Unlicensed and off-label use of medicines at a neonatology clinic in Italy. Pharm World Sci 2007;29(4):361–7 [Epub March 10, 2007].
[2] Shah SS, Hall M, Goodman DM, Feuer P, Sharma V, Fargason Jr C, et al. Off-label drug use in hospitalized children. Arch Pediatr Adolesc Med 2007;161(3):282–90.
[3] Stewart D, Rouf A, Snaith A, Elliott K, Helms PJ, McLay JS. Attitudes and experiences of community pharmacists towards paediatric off-label prescribing: a prospective survey. Br J Clin Pharmacol 2007;64(1):90–5.
[4] Cras A, Conscience MA, Rajzbaum G, Lillo-Le Louet A, Lopez N, Tersen I, et al. Off-label prescribing in a French hospital. Pharm World Sci 2007:97–100.
[5] Di Paolo ER, Stoetter H, Cotting J, Frey P, Gehri M, Beck-Popovic M, et al. Unlicensed and off-label drug use in a Swiss paediatric university hospital. Swiss Med Wkly 2006;136(13-14):218–22.
[6] Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr 2005;164(9):552–8.
[7] Regulation (EC) n. 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use. Official Journal of the European Union 27.12.2006, L378/20-L378/21.
[8] Regulation (EC) n. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union 27.12.2006, L378/1-L378/19.
[9] Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000;32(4):1008–15.

[10] Powell C. The Delphi technique: myths and realities. J Adv Nutr 2003;41(4):376–82.
[11] McKenna HP. The Delphi technique: a worthwhile research approach for nursing? J Adv Nurs 1994;19(6):1221–5.
[12] Lynn MR, Layman EL, Englebardt SP. Nursing administration research priorities. A national Delphi study. J Nurs Admin 1998;28(5):7–11.
[13] Task-force in Europe for Drug Development for the Young (TEDDY) Network of Excellence, www.teddyoung.org (last accessed 21 October 2008).
[14] Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonatal Ed 1999;80(2):F142–4 [discussion F144-5].
[15] Avenel S, Bomkratz A, Dassieu G, Janaud JC, Danan C. The incidence of prescriptions without marketing product license in a neonatal intensive care unit. Arch Pediatr 2000;7(2):143–7.
[16] Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. BMJ 2000;320(7227):79–82.
[17] Gavrilov V, Lifshitz M, Levy J, Gorodischer R. Unlicensed and off-label medication use in a general pediatrics ambulatory hospital unit in Israel. Isr Med Assoc J 2000;2(8):595–7.
[18] t Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN. A survey of the use of off-label and unlicensed drugs in a Dutch children's hospital. Pediatrics 2001;108(5):1089–93.
[19] t Jong GW, van der Linden PD, Bakker EM, van der Lely N, Eland IA, Stricker BH, et al. Unlicensed and off-label drug use in a paediatric ward of a general hospital in the Netherlands. Eur J Clin Pharmacol 2002;58(4):293–7 [Epub June 15, 2002].
[20] Pandolfini C, Impicciatore P, Provasi D, Rocchi F, Campi R, Bonati M, Italian Paediatric Off-label Collaborative Group. Off-label use of drugs in Italy: a prospective, observational and multicentre study. Acta Paediatr 2002;91(3):339–47.
[21] Dick A, Keady S, Mohamed F, Brayley S, Thomson M, Lloyd BW, et al. Use of unlicensed and off-label medications in paediatric gastroenterology with a review of the commonly used formularies in the UK. Aliment Pharmacol Ther 2003;17(4):571–5.
[22] Conroy S, Newman C, Gudka S. Unlicensed and off label drug use in acute lymphoblastic leukaemia and other malignancies in children. Ann Oncol 2003;14(1):42–7.
[23] Neubert A, Dormann H, Weiss J, Egger T, Criegee-Rieck M, Rascher W, et al. The impact of unlicensed and off-label drug use on adverse drug reactions in paediatric patients. Drug Safety 2004;27(13):1059–67.
[24] Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. BMJ 1998;316(7128):343–5.
[25] McIntyre J, Conroy S, Avery A, Corns H, Choonara I. Unlicensed and off label prescribing of drugs in general practice. Arch Dis Child 2000;83(6):498–501.
[26] Craig JS, Henderson CR, Magee FA. The extent of unlicensed and off-label drug use in the paediatric ward of a district general hospital in Northern Ireland. Ir Med J 2001;94(8):237–40.
[27] Carvalho PR, Carvalho CG, Alievi PT, Martinbiancho J, Trotta EA. Prescription of drugs not appropriate for children in a Pediatric Intensive Care Unit. J Pediatr Rio J 2003;79(5):397–402.
[28] Conroy S, Peden V. Unlicensed and off label analgesic use in paediatric pain management. Paediatr Anaesth 2001;11(4):431–6.
[29] Ekins-Daukes S, Helms PJ, Simpson CR, Taylor MW, McLay JS. Off-label prescribing to children in primary care: retrospective observational study. Eur J Clin Pharmacol 2004;60(5):349–53 [Epub May 14, 2004].
[30] Helms PJ, Ekins Daukes S, Taylor MW, Simpson CR, McLay JS. Utility of routinely acquired primary care data for paediatric disease epidemiology and pharmacoepidemiology. Br J Clin Pharmacol 2005;59(6):684–90.
[31] Bucheler R, Schwab M, Morike K, Kalchthaler B, Mohr H, Schroder H, et al. Off label prescribing to children in primary care in Germany: retrospective cohort study. BMJ 2002;324(7349):1311–2.
[32] O'Donnell CP, Stone RJ, Morley CJ. Unlicensed and off-label drug use in an Australian neonatal intensive care unit. Pediatrics 2002;110(5):e52.
[33] European Medicine Agency (EMEA), Doc. Ref: EMEA/166900/2007, Personal Communication, April 17, 2007.
[34] Sinha Y, Cranswick NE. How to use medicines in children: principles of paediatric clinical pharmacology. J Paediatr Child Health 2007;43(3):107–11.
[35] Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr 1999;88:965–8.
[36] Waller DG. Off-label and unlicensed prescribing for children: have we made any progress? Br J Clin Pharmacol 2007;64:1–2.
[37] Dunne J. The European Regulation on medicines for paediatric use. Paediatr Respir Rev 2007;8:177–83.
[38] Hsien L, Breddemann A, Frobel AK, Heusch A, Schmidt KG, Laer S. Off-label drug use among hospitalised children: identifying areas with the highest need for research. Pharm World Sci 2008.
[39] Yoon EY, Dombkowski KJ, Rocchini A, Lin JJ, Davis MM. Off-label utilization of antihypertensive medications in children. Ambul Pediatr 2007;7:299–303.
[40] Volkers AC, Heerdink ER, van DL. Antidepressant use and off-label prescribing in children and adolescents in Dutch general practice (2001–2005). Pharmacoepidemiol Drug Safety 2007;16:1054–62.
[41] McCowan C, Hoskins G, Neville RG. Clinical symptoms and 'off-label' prescribing in children with asthma. Br J Gen Pract 2007;57:220–2.