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Off-label pediatric medicines in Spain☆

Roi Piñeiro Pérez*, Esmeralda Núñez Cuadros, Belén Rodríguez Marrodán, Raquel Escrig Fernández, María Ángeles Gil Lemus, Santiago Manzano Blanco, Cristina Calvo

Comité de Medicamentos de la Asociación Española de Pediatría (CM-AEP), Madrid, Spain

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Abstract Since 2009, the use of off-label and unlicensed drugs has been regulated in Spain. In pediatrics, this exceptional use is more common than in other medical specialties. It varies from 10% to 90% of all prescriptions in children. This variability is due to differences in methodology, classification and sources of information used, and also to the different pediatrics subspecialties. In addition, the knowledge of several pediatricians on this issue is limited and more than half do not comply with the law, in many cases due to ignorance. However, the use of off-label and unlicensed drugs is legal and necessary. The Medicines Committee of the Spanish Association of Pediatrics (CM-AEP) considers that it is necessary to improve the existing information on medicines in the pediatric population. Therefore, the CM-AEP works out a document where suggestions and actions are proposed to achieve it, because children's health deserves it.

PALABRAS CLAVE
Uso *off-label*;
Uso *unlicensed*;
Uso de medicamentos;
Legislación de medicamentos;
Niños

Medicamentos fuera de ficha técnica en Pediatría

Resumen El uso de medicamentos en condiciones diferentes de las establecidas en su ficha técnica está regulado en España desde 2009. En Pediatría, este uso excepcional es más frecuente que en otras especialidades médicas. El porcentaje de uso de medicamentos en situaciones especiales varía entre el 10 y el 90% del total de las prescripciones en niños. Esto es debido a las diferencias en la metodología, clasificación y fuentes de información empleadas y también a las diferentes áreas de capacitación específicas. Además, el conocimiento por parte de los pediatras sobre este asunto es limitado y más de la mitad no se ajusta a la normativa, en muchos casos por desconocimiento. Sin embargo, el uso de medicamentos en esta situación es legal

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* Corresponding author.
E-mail address: roi.pineiro@hgvillalba.es (R. Piñeiro Pérez).

y necesario. El Comité de Medicamentos de la Asociación Española de Pediatría considera que es necesario mejorar la información existente sobre medicamentos en población pediátrica. Por ello, elabora el presente documento en el que realiza sugerencias y propone acciones para lograrlo, porque la salud de los niños lo merece.

Introduction and definitions

Royal Decree 1015/2009 regulates the availability of drugs in special situations in Spain.[1] It establishes rules for compassionate use of drugs undergoing clinical trials, drugs authorised in other countries but not in Spain and drugs used under conditions other than those established in the summary of product characteristics (SmPC). In regard to the latter, the decree specifies that such use would be exceptional and limited to situations where there is no authorised drug that could be used as an alternative in a given patient, adhering to established restrictions regarding the prescription and/or dispensation of the drug and the treatment protocols of the health care facility. The physician in charge must document an appropriate justification of the need for the drug in the health record and inform the patient of its potential benefits and risks, obtaining consent as required by Law 41/2002 of 14 November. According to this law, ''Consent will generally be verbal. However, it will be obtained in writing in the following cases: surgical intervention, invasive diagnostic and therapeutic procedures and, in general, for any use of procedures that involve risks or disadvantages known to have a deleterious effect on the health of the patient.''[2]

The term *exceptional* implies an exception to the rule, but not infrequent use. The information offered in the SmPC of paediatric drugs is often insufficient, incomplete and outdated.[3] Current regulations do not address some of the situations commonly experienced in clinical practice. For instance:

- If authorised drugs are available as an alternative but the scientific evidence shows that an unauthorised treatment is more effective or efficient, which one should be used?
- What are the potential risks of using a drug under conditions other than those authorised in the SmPC? Are they known to have a predictable negative impact on the health of the patient? Does verbal consent from the parents or legal guardians suffice?
- Are paediatricians aware of when they are prescribing a drug outside the conditions established in the SmPC or that is not approved in Spain?

In this document, the Committee on Medicines (CM) of the Asociación Española de Pediatría (Spanish Association of Paediatrics, AEP) seeks to clarify these and other concerns and propose potential solutions to improve the availability of data on drugs used in the paediatric population.

Is it easy to classify a prescription as unauthorised or covered by the SmPC?

The results of previous studies are widely heterogeneous as a result of differences in methodology, classification criteria and sources.[4] Most authors apply the criteria proposed by Turner et al.,[5] who defined off-label (OL) as drugs that are used outside the terms of their product licence that apply to indication, age, dose, or route of administration, and unlicensed (UL) as drugs not yet licensed, specifically contraindicated in children, used in a modified formulation or for which there is no data on its use in the paediatric age group.

The main barrier to the inclusion of indications for paediatric use in the SmPC is the lack of specific clinical trials in the paediatric population. This is due to[6]:

- Difficulties in designing paediatric trials.
- The complex and particular ethical issues involved in research in children.
- The time required to complete the follow-up required in trials in children, which is longer compared to adult trials.
- The protracted drug authorization processes.
- Cost of performing the trials.

The proportion of drugs that lack specific indications for use in paediatrics is large (50%–90%). Approximately 150 million inhabitants in the European Union are aged less than 18 years. Given these circumstances, the unauthorised use of drugs is simply necessary.[6] A review published in 2018 found that more than 80% of paediatric patients received OL drugs and more than 70% received UL drugs.[7]

Paediatricians have the duty to manage children as well as possible, which invariably involves the unauthorised use of drugs. Paediatricians are forced to seek accurate and updated information on the drug from other sources,[8] as the intended use is not included in the SmPC. This problem is addressed by examining clinical trials with variable levels of evidence, clinical guidelines, expert consensus documents, books and specific databases such as Cochrane, Lexicomp or Harriet Lane.[8] Preferably, databases belonging to the specific country will be consulted. One example in the case of Spain, would be Pediamécum.[9]

Are these prescriptions common in paediatrics? Which are the paediatric specialities in which they are most frequent?

Most studies agree that the highest proportion of OL prescriptions are found in the field of neonatology.[4,10,11] Sucasas Alonso et al.[10] found a proportion of OL prescription of 22.5%, while Arocas Casañ et al.[11] found a proportion of 41.4%. When it comes to the type of drug based on the Anatomical Therapeutic Chemical (ATC) classification of active substances, the highest proportion of OL prescriptions corresponds to antiinfective drugs,[4,11] although Sucasas Alonso et al.[10] found a higher proportion of drugs acting on the alimentary tract and metabolism. Off-label prescription was more frequent in surgical patients, very preterm infants and patients with a length of stay greater than 1 week, corresponding to the most vulnerable population.[10]

In paediatric intensive care units (PICUs), exposure to unauthorised drugs is also frequent. Blanco-Reina et al.[4] reported a proportion of OL prescription of 52%, mainly due to doses (79%) or indications (13.5%) outside those specified in the SmPC. When it came to the type of drug, antiinfective drugs were once again the group most frequently prescribed under these conditions (80.2%), followed by drugs acting on the nervous system (63%), which can be attributed to the need for sedation and analgesia characteristic of the PICU. García-López et al.[6] found 53.9% of prescriptions were OL, most frequently on account of the indication (55.7%), followed by age (31.2%). The analysis by age group showed that the use of drugs under conditions not approved in the SmPC decreased with age (63% in patients aged <2 years *vs* 45.2% in patients aged 13 years and older). In this instance, the most frequent group was drugs acting on the cardiovascular system, followed by drugs acting on the nervous system.

Few studies on the subject have focused on the primary care setting. Another study conducted by Blanco-Reina et al.[12] found a proportion of OL prescription of 27.4%, most frequently due to age (60%) and of drugs acting on the respiratory system (63%). In regard to the latter, Suarez-Castañón[13] reported that 85% of cold medicines were prescribed under conditions outside the SmPC, most frequently corresponding to cough medicines, with the most frequent reason for classification as unauthorised being age, especially in children aged less than 2 years, followed by indication.

When it comes to UL prescription, the frequency in Spain, which ranges between 5% and 8%, is lower compared to other developed countries, with frequencies ranging between 10% and 15%.[4,10–12] Most of these prescriptions in Spain are classified as UL due to the preparation of the drug, for instance through compounding. Thus, the percentage of UL prescriptions may be influenced by the pharmaceutical practices in each country and the availability of specific formulations for the paediatric population.

Lastly, a large study conducted in the United States to analyse the use of OL drugs in children aged less than 18 years found that OL prescription was mainly associated with young age, long lengths of stay and severe disease.[14]

Are paediatricians aware of when they are prescribing a drug under unauthorised conditions?

The CM-AEP already posed this question to paediatricians that were members of the AEP or any of its subsidiary speciality and regional societies between July 2012 and March 2013. Six hundred and seventy-three paediatricians participated in a survey conducted by means of an online questionnaire.[3]

Of all respondents, 71.5% reported knowing what OL meant. Also, 61% were aware of prescribing drugs outside the conditions established in the SmPC, and 47% knew that this needed to be documented in the health record. However, barely half informed the parents of it, and only 22% documented it in the health record.

That is, based on these findings, 4 out of 10 paediatricians in Spain did not know when they were prescribing a drug under unauthorised conditions and only 2 out of 10 adhered to current regulations. It became evident that Spanish paediatricians needed to change. In addition, the CM-AEP considers the ongoing effort to develop consensus documents and clinical practice guidelines to increase the information regarding the efficacy and safety of OL drug prescription in children a priority with the goal of including these uses in the conditions authorised under the SmPC.

In 2013, the Pediamécum of the AEP featured up to 384 uses outside the conditions established in the SmPC in its 634-drug database. Many consensus documents and clinical practice guidelines have been published since. In 2020, the number of active substances registered in Pediamécum[9] was 672, and the number of documented OL uses had increased to 411.

This document includes 2 tables on active substances commonly used in paediatrics. We analysed substances with known uses outside the SmPC that are either documented (Table 1) or not documented (Table 2) in the Pediamécum database at the time of the last update of the corresponding drug datasheet.

Is off-label prescription legal?

The use of medicines under unauthorised conditions is appropriate and, as research in children shows, often necessary. In many instances there is no authorised drug for a given treatment goal, or those available are less appropriate for a given patient. Therefore, OL drug prescription is legal and is in the scope of *lex artis ad hoc*. In other words, it is a good medical practice based on up-to-date scientific evidence and diagnosis and treatment protocols. Nevertheless, such use is outside the conditions guaranteed by drug regulatory authorities and, should a claim be made, the pharmaceutical company would not be liable.[3,15]

Paediatricians must be aware that the goal is for the treatment to benefit the patient and should convey this to the parents. This is why it is important to justify OL prescription based on current evidence and clinical practice, document the justification in the health records and obtain consent, at least verbally, from the parents or legal guardians.[3] It is also important that paediatricians are informed and made aware of the need to notify as a sus-

Table 1 Active substances commonly used in paediatrics for which, at the time of the latest update, there was at least one use under unauthorised conditions registered in Pediamécum, and description of the unauthorised use.

Active substance	Use outside the conditions of the SmPC
Methylprednisolone aceponate (topical)	Age <4 months
Acyclovir	Frequent off-label use due to indication. See SmPC
Acetylsalicylic acid	Age <16 years
	Kawasaki disease
	Others, see datasheet
Valproic acid	Prevention of migraines
Adrenaline	Endotracheal route of administration
	Upper airway obstruction
Almagate	Age <6 years
Azithromycin	Intravenous route of administration
	Chronic *Pseudomonas* infection in cystic fibrosis
	Other, see datasheet
Inhaled budesonide	Age <6 months
	Bronchopulmonary dysplasia in infants and preterm infants
Carbamazepine	Maintenance therapy in recurrent mood disorders and conduct disorders
Cefixime	Treatment of urinary tract infection, given on day 1 at 16 mg/kg/day in doses every 12 h, followed by the customary dose of 8 mg/kg/day in doses every 12 or 24 h
	Uncomplicated gonorrhoea
Ceftazidime	In inhaled form for chronic infection by *Burkholderia cepacia* in cystic fibrosis
Ceftriaxone	Chemoprophylaxis of contacts of patients with invasive meningococcal disease
Cefuroxime-axetil	Age <3 months
Ciprofloxacin	Numerous off-label uses. See datasheet
Cyproheptadine	Age <2 years
Clarithromycin	Intravenous route of administration
	Age <6 months
	Treatment and prophylaxis of infection by *Mycobacterium avium complex*
	Helicobacter pylori eradication therapy
	Other, see datasheet
Cotrimoxazole	Age <6 weeks, save for treatment and prophylaxis of pneumonia caused by *Pneumocystis jirovecii*
Desloratadine	Age <1 year
Desmopressin	Central diabetes insipidus in children under 12 years
	Primary nocturnal enuresis in children under 5 years
	Other, see datasheet
Dexamethasone	Infectious upper respiratory disease with breathing difficulty
	Adjuvant therapy for bacterial meningitis
	Other, see datasheet
Dextromethorphan	Age <2 years
Diazepam	Age <6 months
Diclofenac	Age <14 years
	Ophthalmic use to reduce inflammation of the anterior chamber, pain and photophobia
	Intramuscular administration in children
Diphenhydramine	Numerous off-label uses. See datasheet
Digoxin	Foetal supraventricular tachycardia
Dobutamine	Heart failure after cardiac arrest
	For use in newborns, see datasheet
Domperidone	Age <12 years or body weight <35 kg
Doxycycline	Age <8 years (except for treatment of anthrax exposure)
Ebastine	Age <2 years
Enalapril	Age <6 years or body weight <20 kg
	Heart failure
	Proteinuria, nephrotic syndrome
Erythromycin	Prokinetic for gastrointestinal feeding intolerance in newborns

Table 1 (*Continued*)

Active substance	Use outside the conditions of the SmPC
Esomeprazole	Age <4 years, except for treatment of gastro-oesophageal reflux disease, for which its use is authorised starting from age 1 year
	Other, see datasheet
Ethambutol	Age <8 years
	Infections by atypical mycobacteria
Phenytoin	Atrial and ventricular arrythmias, especially if caused by digitalis toxicity
Fentanyl	Age <2 years
Fluconazole	Prophylaxis in very low birth weight preterm infants
Fosfomycin trometamol	Age <6 years
Gentamicin	Intrathecal or intraventricular administration
Hydrocortisone	Hypoglycaemia refractory to continuous infusion of glucose
	Septic shock
	Refractory hypotension
	Other, see datasheet
Ibuprofen	Age <3 months
	Treatment de la juvenile idiopathic arthritis in infants under 6 months
	Other, see datasheet
Ipratropium	Preterm newborns and infants with bronchopulmonary dysplasia
Ketamine	Oral route
	Nasal route
	Status asthmaticus
	Neuropathic pain
Ketorolac	Age <18 years
Levetiracetam	Use as monotherapy in children under 16 years
	Concomitant treatment in newborns aged less than 1 month
	Migraine prophylaxis
	Other, see datasheet
Levofloxacin	Age <18 years
	Second-line treatment of multidrug-resistant tuberculosis
Loperamide	Age <2 years
Loratadine	Age <2 years
Macrogol 3350 + electrolytes	Age <2 years
	Faecal impaction in children under 5 years
Mebendazole	Age <2 years
	Treatment of angiostrongyliasis and trichinosis
Melatonin	Age <18 years
Metamizole	Newborns and infants aged <3 months or with body weight <5 kg
	Oral use of parenteral formulation
	Continuous intravenous infusion
Methylphenidate	Age <6 years
	Symptomatic treatment of hypersomnia and/or narcolepsy
Metronidazole	Combined therapy for *Helicobacter pylori* eradication
Midazolam	Intravenous delivery in infants aged <6 months
	Buccal administration in infants aged <3 months
Morphine	Prolonged treatment of severe chronic pain or postoperative pain in infants aged <1 year
Naloxone	Opioid-induced pruritus
Omeprazole	Age <1 year
	Intravenous administration
	Other, see datasheet
Ondansetron	Age <2 years
	Cyclic vomiting syndrome
	Recurrent vomiting associated with acute gastroenteritis
	Other, see datasheet
Oxybutynin	Age <5 years
Pyrantel pamoate	Age <6 months
Paracetamol	Closure of patent ductus arteriosus in preterm infants
Penicillin G (benzylpenicillin)	Lyme disease

Table 1 (*Continued*)

Active substance	Use outside the conditions of the SmPC
Permethrin	Age <2 months
Benzoyl peroxide	Age <12 years
Prednisolone	Prophylaxis of chemotherapy-induced nausea and vomiting
	Graft-versus-host disease
Prednisone	Prophylaxis of chemotherapy-induced nausea and vomiting
	Graft-versus-host disease
Propofol	Induction and maintenance of general anaesthesia in infants aged less than 1 month
	Sedation in intensive care units in children under 16 years
	Superficial sedation for surgical and diagnostic procedures at any paediatric age
	Antiemetic at very low doses
Propranolol	Use of delayed-release formulations
	Other, see datasheet
Racecadotril	Age <3 months
	Chronic diarrhoea
	Antibiotic-associated diarrhoea
Ranitidine	Oral use in children under 3 years
	Intravenous use is infants aged <6 months
	Oral administration for prophylaxis of stress ulcers
Rifampicin	Treatment of infections by nontuberculous mycobacteria
Risperidone	Treatment of conduct problems in children under 5 years with autism spectrum disorder
Rocuronium	Use as muscle relaxant to facilitate endotracheal intubation during rapid sequence induction and as an adjuvant in the intensive care unit to facilitate intubation and mechanical ventilation
Salbutamol	Nebulization in children under 4 years
Oral rehydration salts	Acidosis and ketosis
Ferrous sulphate and ferrous glycine sulphate	Supplement during the use of epoetin
Tetracycline	Age <8 years
Tobramycin	Inhaled for treatment of chronic pulmonary infection by *Pseudomonas aeruginosa* in children with cystic fibrosis aged <6 years
Topical tretinoin	Use in combination with clindamycin in children under 12 years
	Used as monotherapy in any paediatric age group
Trimethoprim	Age <1 year
Valaciclovir	Age <12 years
	Treatment of herpes zoster and herpes zoster ophthalmicus
	Other, see datasheet
Valganciclovir	Age <18 years
Vancomycin	Intrathecal or intraventricular administration
Voriconazole	Age <2 years
	Other, see datasheet

pected adverse drug reaction any unexpected adverse event following use of a drug under unauthorised conditions. Malpractice and its potential legal ramifications could result from not performing these actions, but never from the mere OL or OL prescription of a drug.[3,15]

Is it safe to prescribe drugs outside authorised conditions?

The use of pharmaceuticals under unauthorised conditions may lead to the development of adverse effects not previously described or ineffective treatment. Thus, this practice is not always safe.[16,17] However, as noted above, it is the ethical duty of paediatricians to keep their knowledge of the evidence up to date in order to offer patients the best possible treatment.

The pharmacokinetics and pharmacodynamics of drugs are different in children compared to adults and vary based on age, body weight and developmental stage. These differences entail the need of prescribing different doses (based on age or body weight) to achieve the expected effectiveness. In the case of OL prescription in children, this may need to be done by extrapolating data obtained in other age groups, which may lead to differences in the effectiveness or safety of the drug.[18]

Table 2 Active substances commonly used in paediatrics for which, at the time of the latest update, there was no use under unauthorised conditions registered in Pediamécum.

Amoxicillin
Amoxicillin-clavulanic acid
Ampicillin
Atropine
Caffeine
Cefadroxil
Cefotaxime
Cefuroxime
Clindamycin
Clotrimazole
Cloxacillin
Cholecalciferol
Dopamine
Phenobarbital
Phenoxymethylpenicillin
Fosfomycin calcium
Furosemide
Calcium gluconate
Hydrochlorothiazide
Isoniazid
Methylprednisolone
Nystatin
Oseltamivir
Pyrazinamide

However, and despite efforts made in recent years to increase and improve the development of drugs for use in children,[19] there are still many situations in which the paediatrician has to resort to OL or UL prescription to offer patients the best possible treatment.[4,10–12] Therefore, it is essential that paediatricians not only keep in mind the legal conditions for OL drug prescription, but also the *do no harm* principle, weighing the benefits and risks at the time of prescription, during treatment and in the subsequent follow-up, actively reporting adverse events associated with the use of drugs under these conditions and including parents and, should age allow, the patients in the decision-making process.

While in many situations the OL prescription of drugs in paediatrics is supported in scientific and clinical evidence that provides some assurance about their use, there are also situations in which the available data are much scarcer. This is particularly common in the prescription of recently marketed drugs, high-risk drugs, used in the most vulnerable subsets of the paediatric population or through routes of administration that carry a higher risk of adverse reactions. All of them are situations requiring careful evaluation and follow-up of pharmaceutical treatment.

Another aspect to consider is that the use of drugs not meant for paediatric patients may result in the administration of excipients that are not appropriate for certain age groups, especially newborn infants, or patients with underlying disease or intolerance.[20–22] To determine their presence, it may be useful to consult databases that provide this information, such as the Safety and Toxicity of Excipients for Paediatrics (STEP),[23] or to consult directly with the pharmacist.

Do we need to improve the available information on drugs used in the paediatric population? Proposals of the CM-AEP and conclusions

Considering all of the above, the answer seems evident. Children are a vulnerable population that must be protected. There is no better way to do this than to promote high-quality research in the paediatric field so that appropriate drugs are available with fitting formulations and tested in the paediatric population.

In 2007, Europe developed specific regulations to protect the health of children. This gave rise to paediatric investigation plans, research and development programmes intended to guarantee the generation of the necessary data to establish the conditions under which a drug may be authorised for use in the paediatric population.[24] Ten years later, the results of this strategy were evaluated.[25] Although there was a significant increase in research in the paediatric field and new indications for use were authorised, the impact was not as expected, and there is still considerable room for improvement. This should translate to a reduce use of drugs under OL conditions, but, to put an example, the data on the use of pharmaceuticals outside the conditions established in the SmPC registered in Pediamécum in Spain show no such reduction.[9] To increase the efficiency of regulatory measures and the development of more drugs specifically intended for the paediatric population, the European Medicines Agency (EMA) published an action plan in 2018 to identify the medical needs of the paediatric population and to increase transparency in everything related to drugs used in children, among other objetives.[26]

Clinical trials in children are necessary, but also complicated. This type of research must be promoted zealously, establishing collaborative networks focused on research in children, such as the Red Española de Ensayos Clínicos en Pediatría[27] (RECLIP), which leads paediatric clinical trials in Spain. New clinical trial designs must be developed to include the adolescent population from the outset. The administration should explicitly promote these initiatives by offering real support to these networks so that they do not depend exclusively on clinical trials funded by the pharmaceutical industry. Many drugs that are of little interest to the industry due to their low market price or the target population being too small could be investigated in independent clinical trials if there was adequate support of paediatric research.

It is also important to undertake studies of a different kind, multicentre studies focused on different diseases of childhood, which are often rare and require a concerted effort to get significant results in a population that is smaller compared to adult diseases. Networking in different paediatric specialities is a strongpoint of paediatrics that is developing significantly in Spain and allows the collection of data that could not be obtained otherwise, producing evidence on treatment with drugs outside authorised conditions.[28] There are numerous examples of networks on specific subjects in Spain, as evinced in some recent publications.[29] In short, research in the paediatric population must be pursued to gain knowledge on the drugs

appropriate for use in this age group, combining every possible resource, whether public or private.

We must also emphasise the need to report potential adverse effects through the national pharmacological surveillance network. In 2018, the EMA published a guideline on good pharmacovigilance practices with a chapter devoted to the paediatric population. The guideline explicitly established that the use of medicines under unauthorised conditions can expose paediatric patients to an increased risk of adverse effects and medication errors.[30] The notification of adverse events to the national pharmacological surveillance network is an excellent tool to contribute to the available information on the use of drugs in uncertain scenarios.

On the other hand, it is essential that the knowledge of paediatricians as to what constitutes use of a drug outside the authorised conditions, the current legislation on the subject and how to do it safely improves. Initiatives such as those advanced by the Asociación Española de Pediatría and its flagship journal, ANALES DE PEDIATRÍA, to educate and inform paediatricians, are among the many tools that can improve this knowledge. Paediatrics manuals and handbooks, and Pediamécum[9] as an example of such sources, must always note whether there is evidence supporting the OL use of a drug in the paediatric population and provide the prescriber all the available information. Specific training of paediatricians through educational platforms such as Continuum[31] can also offer valuable knowledge on this subject to all prescribers. Making a difficult subject such as this one appealing is also an important challenge. The health of children deserves this effort.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.anpedi.2020.12.008.

References

1. Real Decreto 1015/2009 por el que se regula la disponibilidad de medicamentos en situaciones especiales. Boletín Oficial del Estado número 174 de lunes 20 de julio del 2009 [Accessed 1 November 2020]. Available from: https://www.boe.es/boe/dias/2009/07/20/pdfs/BOE-A-2009-12002.pdf.
2. Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica. Boletín Oficial del Estado número 274 de 15 de noviembre del 2002. Referencia: BOE-A-2002-22188 [Accessed 1 November 2020]. Available from: https://www.boe.es/buscar/pdf/2002/BOE-A-2002-22188-consolidado.pdf.
3. Piñeiro Pérez R, Ruiz Antorán MB, Avendaño Solá C, Román Riechmann E, Cabrera García L, Cilleruelo Ortega MJ, et al. Conocimiento sobre el uso de fármacos off-label en pediatría. Resultados de una encuesta pediátrica nacional 2012–2013 (estudio OL-PED). An Pediatr (Barc). 2014;81:16–21.
4. Blanco-Reina E, Medina-Claros AF, Vega-Jiménez-Riola MA, Ocaña-Riola R, Márquez-Romero EI, Ruiz-Extremera A. Utilización de fármacos en niños en cuidados intensivos: estudio de las prescripciones off-label. Med Intensiva. 2016;40:1–8.
5. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. BMJ. 1998;316:343–5.
6. García-López I, Fuentes-Ríos JE, Manrique-Rodríguez S, Fernández-Llamazares CM. Utilización de medicamentos en condiciones off-label y unlicensed: resultados de un estudio piloto realizado en una unidad de cuidados intensivos pediátrico. An Pediatr (Barc). 2017;86:28–36.
7. Moulis F, Durrieu G, Lapeyre-Mestre M. Off-label and unlicensed drug use in children population. Therapie. 2018;73:135–49.
8. Frattarelli DA, Galinkin JL, Green TP, Johnson TD, Neville KA, Paul IM, et al. American Academy of Pediatrics Committee on Drugs. Off-label use of drugs in children. Pediatrics. 2014;133:563–7.
9. Asociación Española de Pediatría. Pediamécum [Accessed 1 December 2020]. Available from: https://www.aeped.es/comite-medicamentos/pediamecum.
10. Sucasas Alonso A, Avila-Alvarez A, Combarro Eiriz M, Martínez Roca C, Yáñez Gómez P, Codias López A, et al. Uso de medicamentos en condiciones no aprobadas en cuidados intensivos neonatales. An Pediatr (Barc). 2019;91:237–43.
11. Arocas Casañ V, Cabezuelo Escribano B, Garrido-Corro B, de la Cruz Murie P, Blázquez Álvarez MJ, de la Rubia Nieto MA. Utilización de medicamentos fuera de ficha técnica y sin licencia en una Unidad de Cuidados Intensivos Neonatales Española. Farm Hosp. 2017;41:371–81.
12. Blanco-Reina E, Vega-Jiménez MA, Ocaña-Riola R, Márquez-Romero EI, Bellido-Estévez I. Estudio de las prescripciones farmacológicas en niños a nivel de atención primaria: evaluación de los usos off-label o fuera de ficha técnica. Aten Primaria. 2015;47:344–50.
13. Suarez-Castañón C. Uso de anticatarrales en menores de 14 años en consultas de Atención Primaria. An Pediatr (Barc). 2016;84:10–7.
14. Yackey K, Stukus K, Cohen D, Kline D, Zhao S, Stanley R. Off-label medication prescribing patterns in pediatrics: an update. Hosp Pediatr. 2019;9:186–93.
15. Álvarez Escudero J, Paredes Esteban RM, Cambra Lasaosa FJ, Vento M, López Gil M, de Agustín Asencio JC, et al. Más de 3 horas y menos de 3 años: Seguridad de procedimientos anestésicos en menores de 3 años sometidos a cirugía de más de 3 horas. An Pediatr (Barc). 2017;87, 236.e1–236.e6.
16. Evidence of harm from off-label or unlicensed medicines in children. EMEA/126327/2004. Updated 2004 [Accessed 1 December 2020]. Available from: https://www.ema.europa.eu/en/documents/other/evidence-harm-label-unlicensed-medicines-children_en.pdf.
17. Pratico AD, Longo L, Mansueto S, Gozzo L, Barberi I, Tiralongo V, et al. Off-label use of drugs and adverse drug reactions in pediatric units: a prospective, multicentre study. Current Drug Safety. 2018;13:200–7.
18. Bouquet E, Star K, Jonville-Bera AP, Durrieu G. Pharmacovigilance in pediatrics. Therapie. 2018;73:171–80.
19. European Commission. State of Paediatric Medicines in the EU. 10 Years of the EU paediatric Regulation. Report from the Commission to the European Parliament and the Council [Accessed 1 December 2020]. Available from: https://ec.europa.eu/health/human-use/paediatric-medicines_en.
20. Turner MA, Duncan JC, Shah U, Metsvaht T, Varendi H, Nellis G, et al. Risk assessment of neonatal excipient exposure: lessons from food safety and other areas. Adv Drug Deliv Rev. 2014;73:89–101.
21. Nellis G, Metsvaht T, Varendi H, Toompere K, Lass J, Mesek I, et al. Potentially harmful excipients in neonatal

medicines: a pan-European observational study. Arch Dis Child. 2015;100:694–9.
22. O'Brien F, Clapham D, Krysiak K, Batchelor H, Field P, Caivano G, et al. Making medicines baby size: the challenges in bridging the formulation gap in neonatal medicine. Int J Mol Sci. 2019;20:2688.
23. European Paediatric Formulation Initiative (EuPFI). Base de datos STEP (Safety and Toxicity of Excipients for Paediatrics) [Accessed 1 December 2020]. Available from: http://www.eupfi.org/step-database-info/.
24. European Medicines Agency. Paediatrics: Regulatory and procedural guidance [Accessed 1 December 20200]. Available from: https://www.ema.europa.eu/en/paediatrics-regulatory-procedural-guidance.
25. Commission to the European Parliament and the Council. State of Paediatric Medicines in the EU. 10 years of the EU Paediatric Regulation. Available from: https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/2017_childrens medicines_report_en.pdf. [Accessed 1 December 2020].
26. European Medicines Agency and European Commission (DG Health and Food Safety) action plan on paediatrics [Accessed 1 December 2020]. Available from: https://www.ema.europa.eu/en/documents/report/european-medicines-agency-european-commission-dg-health-food-safety-action-plan-paediatrics_en.pdf.
27. Spanish Pediatric Clinical Trials Network (RECLIP) [Accessed 1 December 2020]. Available from: http://www.reclip.org/.
28. Morales-Olivas JM. Medicamentos de alto impacto sanitario y económico: el necesario equilibrio entre innovación y sostenibilidad. An Pediatr (Barc). 2019;90:139–40.
29. Calvo C, Sainz T, Codoñer-Franch P, Santiago B, García-García ML, García Vera C, et al. La investigación en Pediatría en España: retos y prioridades. Plataforma INVEST-AEP. An Pediatr (Barc). 2018;89, 314.e1–314.e6.
30. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Product- or population-specific considerations IV: paediatric population [Accessed 1 December 2020]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-product-population-specific-considerations-iv_en-0.pdf.
31. Continuum. El portal de formación de la Asociación Española de Pediatría [Accessed 1 December 2020]. Available from: https://continuum.aeped.es/.