International Journal of Clinical Pharmacy (2022) 44:264–269
https://doi.org/10.1007/s11096-021-01303-5

COMMENTARY

Regulating pediatric off-label uses of medicines in the EU and USA: challenges and potential solutions

Comparative regulation framework of off label prescriptions in pediatrics: a review

Benedetta Guidi[1] · Andrea Parziale[2] · Luca Nocco[3] · Aniello Maiese[4] · Raffaele La Russa[5] · Marco Di Paolo[4] · Emanuela Turillazzi[4]

Received: 8 March 2021 / Accepted: 24 June 2021 / Published online: 8 September 2021

Abstract
Background Off-label uses of medicines are common in pediatrics. The literature reports that at least one-third of children in hospital and up to 90% of newborns in neonatal intensive care units receive off-label prescriptions. Moreover, the lack of data on safety and efficacy in the pediatric population may sometimes increase the risk of adverse drug reactions. *Objective* This paper aims to (a) map the main gaps in the existing EU and US regulatory frameworks for pediatric drug development and off-label use and (b) propose potential solutions for further discussion. *Conclusion* The selected jurisdictions aim to limit off-label prescribing, but implementation levels generally seem low, including in pediatric settings. Subject to further research, we propose potential concerted actions and initiatives of international cooperation to fill this gap. In particular, regulators and pediatric societies could strengthen manufacturers' incentives to develop pediatric medicines, pediatricians' information about off-label uses, and patients' and parents' awareness.

Keywords Ethical and legal implications · European Union · Off-label prescription · Off-patent medicines · Pediatric population · United States

Introduction

Off-label (OL) drug use is a global problem linked to the challenge of delivering an optimal supply of safe drugs to children [1]. Gold-standard clinical trials are often unavailable for pediatric populations. Several barriers may limit children's participation in trials, e.g., parents' practical and emotional concerns [2]. Therefore, drug prescribing to children is often based on extrapolation from clinical trials conducted on adults, a well-established policy in the EU and US [3].

Consequently, in the lack of formulations explicitly approved for pediatric use, pediatricians may prescribe medicines tested on and approved for adults to children, e.g., with a different form and dosage or route of administration [4]. OL uses are estimated to exceed 50% in many therapeutic areas and may be ineffective or even dangerous for children [5]. A 2018 systematic review confirmed that pediatric off-label prescribing remains a common practice [6]. Likewise, Hoon et al. [7] reported that US office-based physicians had ordered systemic drugs OL for children at increasing rates, despite recent efforts to improve evidence and drug approval for pediatric uses. Furthermore, OL use seems higher in neonatal and pediatric intensive care settings and oncology wards than in primary care [8].

The EU and the US have adopted different regulatory approaches to pediatric OL drug use. This article reviews these regulatory efforts to promote pediatric medicinal

Benedetta Guidi and Andrea Parziale have contributed equally to this work.

✉ Benedetta Guidi
benedettaguidi@virgilio.it

1 Clinical and Traslational Science Research Department, University of Pisa, Via Roma 55 1, 56124 Pisa, Italy

2 Eurac Research, Bolzano, Italy

3 Sant'Anna School of Advanced Studies, Pisa, Italy

4 Legal Medicine Section, University of Pisa, Pisa, Italy

5 University of Rome La Sapienza, Rome, Italy

products and limit OL prescribing to minors. We aim to identify the main gaps in the regulatory framework and propose potential solutions for further discussion.

The EU regulatory framework

In the EU, Regulation 1901/2006 (Pediatric Regulation) aims to "facilitate the development and accessibility of medicinal products for use in the pediatric population" and sets out obligations and incentives for pharmaceutical companies. Before applying for marketing authorization (MA), companies must agree to a "pediatric investigation plan" (PIP) with the Pediatric Committee of the European Medicines Agency (EMA). If the PIP is fulfilled, six months are added to the product's patent protection.

The EU Court of Justice states that, in EU law, "[t]here is no provision which prevents doctors from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorization has been granted" [9].

However, the promotion of OL use is prohibited (Article 87, Directive 2001/83). Moreover, marketing authorization holders (MAHs) are required to report adverse events (AEs) from OL use (Directive 2010/84). Finally, manufacturers may be held liable for damages from OL uses if (a) they withheld information on a known AE (warning defect) and (b) the OL use could be "reasonably […] expected" (Article 6, Directive 85/374—Product Liability Directive). OL product liability (PL) litigation is scarce in the EU (see Table 1).

EU member states' regulations on OL uses

In the EU, OL prescriptions are regulated mainly at the national level (see Table 1). A 2017 European Commission study grouped the EU Member States into two main sets [4]:

1. Countries with regulatory and reimbursement policies (France, Hungary, Italy, Lithuania, Netherlands, Spain, and Sweden).
2. Countries with reimbursement policies only (Germany, Greece).

Our comparative review focuses on set 1 (see Table 1). While reimbursement policies may indirectly shape OL practices [9], our research primarily deals with regulations directly addressing OL uses.

France

In the wake of the Mediator *affaire* (2010–2011) [10], *Loi* n. 2011–2012 established a distinctive monitoring system for OL uses in France (*Recommendations temporaires d'utilisations*, RTUs). The French Medicines Agency may issue "Temporary Recommendations For Use" (RTU s) for authorized medicines prescribed OL if data show that the risk–benefit ratio is presumably favorable (Article L. 5121-12-1, *Code de Santé Publique*, CSP). RTUs dictate recommendations on OL uses regarding, e.g., posology, treatment length, and target population; a monitoring protocol detailing the MAH's reporting obligations is included.

Outside the scope of RTUs, OL prescriptions are permitted if in line with "acquired or validated medical knowledge" [11]. The physician must specifically inform the patient that the prescription is OL (Article L. 5121-12-1, III, CPS). If the patient is younger than 18 years, the physician must acquire the legal representative's informed consent (IC) and "take into account" the minor's will (Article R. 4127-42, CSP).

Finally, physicians must report AEs (Article L. 5121-25, CSP). Although failure to report severe AEs is a criminal offence (Article R. 5421-1 CSP) (see Table 1), under-reporting remains a significant issue [12].

Italy

The Italian legislation on OL prescriptions was introduced in the wake of the Di Bella case of 1998 [13]. Law n. 94/1998 (Di Bella Law) allows OL prescriptions only:

(a) In individual cases, under the direct responsibility of the physician.
(b) After acquiring the patient's IC.
(c) If the physician considers that the patient cannot be usefully treated with medicines already approved for the indication in question.
(d) Based on internationally recognized scientific publications reporting the OL use in question.

Law n. 244/2007 specifies that physicians cannot prescribe medicines OL unless completed phase II studies show favorable results (Article 2(348)).

Physicians should inform patients about the OL prescription's risks and benefits [13], although they are not explicitly required to disclose its administrative status (see Table 1). If the patient is younger than 18 years, the physician acquires the parents' IC (Law 219/2017) and considers the minor's will according to their discernment capacity. Finally, physicians must report AEs (Article 22(2), Health Ministry Decree of 30 April 2015). However, failure to report is not sanctioned. Thus, under-reporting represents a significant issue [14].

Despite reported examples of judicial proceedings targeting non-compliant OL prescriptions [13], their impact on pediatric practice seems limited.

Table 1 Comparative regulation framework of off-label prescriptions in Pediatrics

Impact on pharmaceutical industry	Impact on clinical practice
EU	
Pediatric medicine development	Clinical justification
Obligation to submit PIP:	No explicit EU legislation. See national laws below
If PIP is not fulfilled, MA for adult indication is blocked.	IC acquisition
If PIP is fulfilled, 6 months are added to patent protection. If the drug is orphan, 2 years of additional market exclusivity are also granted	No explicit EU legislation. See national laws below
OL prescriptions	AER
Ban on OL promotion	No explicit EU legislation. See national laws below
Requirement to report AE from OL uses	Implementation level
Potential PL for harmful OL use if such use could be 'reasonably expected' and risk was known	See national laws below
Implementation level	
Pediatric medicines development improved, except for children-specific and rare diseases	
OL promotion ban is rarely enforced	
PL litigation is scarce	
France	
Pediatric medicine development	Clinical justification
See the EU section above	Acquired or validated medical knowledge must support OL prescription
OL uses	IC acquisition
Examples of OL PL litigation	Physicians must disclose prescription's OL status to patient
RTU protocols detail MAH's reporting obligations	If patient is younger than 18 years, physician acquires parents' IC and considers minor's will
RTU may include MAH's commitment to extend MA	AER
Implementation level	Physicians must report AEs
Few RTUs are issued	Implementation level
No commitments to extend MA	Physicians may not fulfill requirements, despite examples of civil medical malpractice actions
	AEs are underreported
Italy	
See the EU section above	Clinical justification
	Physician must base OL prescription on favorable phase II studies' results
	IC acquisition
	No legal requirement to disclose prescription's OL status
	If patient is younger than 18 years, physician acquires parents' IC and considers minor's will
	AER
	Physician must report AEsImplementation level
	Pediatric OL prescription is not always supported by sufficient evidence
	AEs are underreported
USA	
Pediatric medicine development	Clinical justification
Obligation to submit PSP	OL uses must be scientifically supported
6 months are added to patent protection	IC acquisition
OL uses	No legal requirement to disclose prescription's OL status to patient
MAHs cannot promote OL uses	Age of consent varies across States
PL for failure to warn if (a) manufacturer promotes OL use and (b) risk is known	AER
Implementation level	AER is voluntary.
Pediatric medicine development improved but OL prescribing remains common	Implementation level
OL promotion is vigorously prosecuted	In specific settings, pediatric patients are exposed to OL uses with uncertain evidence
	AEs are underreported

The US experience

The US pediatric legislation primarily consists of the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA). The former requires companies to submit a Pediatric Study Plan to the FDA for any new product. The latter adds six-month extra exclusivity to the medicine's patent to companies that voluntarily agree with the FDA to conduct pediatric studies (see Table 1).

Such legislation has significantly increased pediatric studies and labels but seems to have had a marginal impact on OL prescriptions in children [15], which remain common. A potential reason for this is that pediatric regulations focus on the development of new medicines. Therefore, they do not adequately incentivize to bring pediatric off-label uses on-label [15]. Another potential reason is that conducting research on children remains challenging [15].

US law bans OL promotion. In particular, manufacturers can be held liable for "failure to warn" if they (a) promote a pediatric OL use and (b) withhold information on a known side effect associated with such use [16].

Litigation also targets pediatricians prescribing OL uses that prove harmful [17]. Courts clarified that physicians:

1. Can prescribe authorized medicines for any scientifically supported use, regardless of the prescription's on-label or OL status.
2. Have no duty to inform patients of a prescription's OL status [18].
3. Must acquire parents' IC if the patient is a minor. Minors' age of consent varies wildly across the States [19].

Nevertheless, pediatric OL uses are not always supported by sufficient evidence [20] and AE underreporting remains an issue [21].

Challenges and potential solutions

The selected jurisdictions share the objective of limiting OL uses by (i) promoting the development of medicines approved for use in children and (ii) setting requirements for lawful OL uses. This paragraph identifies the main challenges undermining each strategy and proposes potential solutions for further discussion (Table 2).

Pediatric medicine legislation

The current EU and US pediatric regulations fail to stimulate the development of medicines for children-specific diseases. Regulators could address this gap under a broader action plan by (a) targeting barriers to recruiting children in clinical trials and (b) providing incentives to companies developing medicines for children-specific diseases.

Sub (a), regulators may provide sponsors and investigators with best practices on pediatric research. Furthermore, regulatory acceptance of innovative research techniques may help. Particularly promising are platform trials, which enable a direct and efficient comparison between different treatments against a common control group [22].

Table 2 Proposed initiatives

Manufacturers
Stimulating development of medicines for children-specific diseases
Regulators' best practices on research in children and regulatory acceptance of platform trials
Dedicated public research funding, improved pediatric research infrastructures, public–private partnerships
Stimulating off-patent drug repurposing
Repurposing framework led by not-for-profit/academic entities
Advocacy campaigns highlighting (a) business opportunities and (b) legal risks for failure to monitor and study pediatric OL uses
Physicians
Improving access to scientific information
Consensus lists of accepted OL uses issued by FDA and EMA
Recommendations and dedicated public research funding on pediatric off-label uses of off-patent medicines
Delivering specific training
Development of learning modules for pediatricians by pediatric societies and expert bodies covering:
Good clinical practice and harms of OL prescriptions
Acquisition of parents' IC and appropriate consideration of children's will
AE reporting
Patients and parents
Improving public awareness
Regulators and pediatric societies' joint information campaigns on benefits and risks of OL uses targeting patients and parents

Sub (b), the European Commission is considering introducing novel rewards, such as transferrable vouchers entitling to priority review [23]. The experience of the US Priority Review Voucher system (Sect. 529, FD&C Act) suggests, however, that such measures are not per se sufficient. In light of this market failure, a more top-down approach may, therefore, be warranted. This may include dedicated public research funding [24], strengthened pediatric research infrastructures, and public–private partnerships.

A related market failure concerns the OL use of off-patent medicines in children. Such products are no longer covered by IP rights and, therefore, are under researched by the industry [7]. Dedicated incentives to the industry to bring such OL uses on-label (e.g., in the EU, through the "paediatric use marketing authorizations" scheme under Article 30, Pediatric Regulation) have not delivered the expected results. Alternatively, a repurposing framework led by not-for-profit or academic organizations, such as proposed by the European Commission expert group on Safe and Timely Access to Medicines for Patients in 2019, may prove helpful [25].

A joint EU-US action along these lines would be beneficial in a two-fold way. Firstly, the exchange of knowledge would provide the EMA and FDA with a large set of data to devise sound policy proposals. Secondly, a joint model legislative proposal would help harmonize the development of pediatric medicine globally, mitigating development and administrative costs for pharmaceutical companies operating in pediatrics.

Pediatric societies could also conduct concerted advocacy initiatives to encourage pharmaceutical companies to improve pediatric OL use and apply for MA extensions. These initiatives could highlight:

1. Business opportunities in researching pediatric OL uses and applying for 'pediatric' MAs.
2. PL risk for failure to monitor and communicate risks associated with pediatric OL uses.

OL regulation

Indeed, evidence emerges that, regardless of the policy model adopted, non-compliance is common in pediatric practice. This suggests that the causes of noncompliance are practical rather than legal, particularly (a) pediatricians' lack of access to scientific information and specific training and (b) patients' and parents' unawareness about OL uses.

Sub (a), first, the FDA and EMA could issue consensus lists of accepted uses in the US and EU, respectively, in line with the EAP and AAP joint policy statement on pediatric OL uses [26]. These lists could be administered by specific pediatric expert groups, receiving scientific support from State-level regulators in collaboration with pediatric societies.

Secondly, physicians would particularly benefit from FDA and EMA recommendations on the off-label use of off-patent products in children, based on established medical use [27]. Dedicated public research funding could also help improve knowledge on the safety of off-patent products [28].

Thirdly, pedagogic efforts by supranational and national pediatric societies may play a role. EU and national pediatric societies and expert bodies could develop learning modules to teach pediatricians:

1. Good clinical practice and harms of OL prescriptions.
2. How to acquire parents' free and IC while appropriately considering children's will.
3. How to appropriately report AEs.

Federal and state-level pediatric societies and expert bodies could promote a similar training initiative in the US. These modules may be implemented in pediatric training programs.

Finally, *sub* (b), regulators and pediatric societies could promote joint information campaigns to educate the public, particularly children and parents, about the benefits and risks of OL uses.

Conclusions

OL drug use in children is widespread, especially in early childhood. From our study emerges that different regulatory models correspond to low implementation levels, with barriers that are more. practical than legal. The international cooperation of stakeholders, including regulatory authorities, could provide a solid basis for harmonic guidance on OL use. Concerted actions may ensure children's right to safe, effective, and quality medicines and prescriptions. Further research is required to detail the proposed solutions.

Acknowledgements The Authors are grateful to the anonymous reviewers for their helpful remarks.

Funding No specific funding was received.

Conflicts of interest The authors declare that there is no conflict of interest.

References

1. Lenk C. Off-label drug use in paediatrics: a world-wide problem. Curr Drug Targets. 2012;13(7):878–84.
2. Russo C, Stout L, House T, Santana VM. Barriers and facilitators of clinical trial enrollment in a network of community-based pediatric oncology clinics. Pediatr Blood Cancer. 2020;67(4):e28023.

3. Schiavone S, Neri M, Pomara C, Riezzo I, Trabace L, Turillazzi E. Personalized medicine in the paediatric population: the balance between pharmacogenetic progress and bioethics. Curr Pharm Biotechnol. 2017;18(3):253–62.
4. European Commission. Study on off-label use of medicinal products in the European Union.
5. Bruxelles. 2017. Available online: https://ec.europa.eu/health/sites/health/files/files/documents/2017_02_28_final_study_report_on_of-label_use_.pdf.
6. Carpenter D, Gonzalez D, Retsch-Bogart G, Sleath B, Wilfond B. Methodological and ethical issues in pediatric medication safety research. Pediatrics. 2017;140(3):e20170195.
7. Allen HC, Garbe MC, Lees J, Aziz N, Chaaban H, Miller JL, et al. Off-label medication use in children, more common than we think: a systematic review of the literature. J Okla State Med Assoc. 2018;111(8):776–83.
8. Hoon D, Taylor MT, Kapadia P, Gerhard T, Strom BL, Horton DB. Trends in off-label drug use in ambulatory settings: 2006–2015. Pediatrics. 2019;144(4):e20190896.
9. Cuzzolin L, Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. Exp Opin Drug Saf. 2006;5(5):703–18.
10. Court of Justice of the EU, 11th June 2015, case T-452/14, Laboratoires CTRS v Commission, EU:T:2015:373, para 79.
11. Einbinder F. Mass torts: dispute resolution in France and the United States: the Vioxx and mediator cases compared. Wash L Rev. 2020;29(3):575–647.
12. Laude A, Mathieu B, Tabuteau D. Droit de la santé. PUF, 2007, n. 410.
13. Durrieu G, Jacquot J, Baudrin D, Mège M, Rousseau V, Bagheri H, et al. Apport de la visite d'assistants de recherche clinique aux cabinets de médecins généralistes sur la notification des effets indésirables médicamenteux [Improving adverse drug reaction reporting by general practitioners through clinical research assistants visits]. Therapie. 2017;72(3):351–5.
14. Guidi B, Nocco, L. The debate concerning the off-label prescriptions of drugs: a comparison between Italian and US law. Op. J, 2011, 1. Available from: http://www.opiniojurisincomparatione.org/opinio/article/view/43.
15. Ferrajolo C, Capuano A, Trifirò G, Moretti U, Rossi F, Santuccio C. Pediatric drug safety surveillance in Italian pharmacovigilance network: an overview of adverse drug reactions in the years 2001–2012. Exp Opin Drug Saf. 2014;13(Suppl 1):S9-20.
16. Corny J, Lebel D, Bailey B, Bussières JF. Unlicensed and off-label drug use in children before and after pediatric governmental initiatives. J Pediatr Pharmacol Ther. 2015;20(4):316–28.
17. Ausness RC. There's danger here, cherie: liability for the promotion and marketing of drugs and medical devices for off-label uses. Brook L Rev. 2008;73:1253–326.
18. Liability and off-label prescriptions. Psychiatry (Edgmont). 2009;6(2):43–4.
19. Mithani Z. Informed consent for off-label use of prescription medications. Virtual Mentor. 2012;14(7):576–81.
20. McNary A. Consent to treatment of minors. Innov Clin Neurosci. 2014;11(3–4):43–5.
21. Czaja AS, Reiter PD, Schultz ML, Valuck RJ. Patterns of off-label prescribing in the pediatric intensive care unit and prioritizing future research. J Pediatr Pharmacol Ther. 2015;20(3):186–96.
22. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29(5):385–96.
23. Park JJH, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials. 2019;20(1):572.
24. European Commission, Inception Impact Assessment, https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-&-rare-diseases-updated-rules_en.
25. Donato Bonifazi: CVBF as EPTRI Coordinator, 06 January 2021, https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-&-rare-diseases-updated-rules/F1411106_en.
26. Christine Dawson: European Social Insurance Platform: ESIP, 06 January 2021, https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-&-rare-diseases-updated-rules/F1408716_en.
27. Schrier L, Hadjipanayis A, Stiris T, Ross-Russell RI, Valiulis A, Turner MA, et al. Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European academy of paediatrics and the European society for developmental perinatal and pediatric pharmacology. Eur J Pediatr. 2020;179(5):839–47.
28. Marika V. FRANCE: Secrétariat général des Affaires européennes, 06 January 2021 https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-&-rare-diseases-updated-rules/F1407901_en.
29. Rita K. Prescrire, 2021. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-&-rare-diseases-updated-rules/F1403036_en.