

Original Article

Open Access



Off-label prescription of medicines: what do we know about the legislation in EU member states?

Renske Caminada, Max Polano, Anna M. G. Pasmooij, Violeta Stoyanova-Beninska

Dutch Medicines Evaluation Board, Utrecht 3531 AH, The Netherlands.

Correspondence to: Dr. Violeta Stoyanova-Beninska, Dutch Medicines Evaluation Board, Graadt van Roggenweg 500, Utrecht 3531 AH, The Netherlands. E-mail: v.stoyanova@cbg-meb.nl

How to cite this article: Caminada R, Polano M, Pasmooij AMG, Stoyanova-Beninska V. Off-label prescription of medicines: what do we know about the legislation in EU member states? *Rare Dis Orphan Drugs J* 2021;1:5.
<https://dx.doi.org/10.20517/rdodj.2021.04>

Received: 11 Nov 2021 **First Decision:** 6 Dec 2021 **Revised:** 15 Dec 2021 **Accepted:** 20 Dec 2021 **Published:** 27 Dec 2021

Academic Editor: Daniel Scherman **Copy Editor:** Xi-Jun Chen **Production Editor:** Xi-Jun Chen

Abstract

Aim: Off-label prescription is not regulated on the European Union (EU) level and therefore not harmonised in the EU Member States (MS). Despite this, the use of medicines outside of the drug label occurs in clinical practice, and it can be included in treatment guidelines and/or reimbursed in some cases. It is, however, currently not clear to what extent off-label use can be included in regulatory discussions at a European level at the different committees at the European Medicines Agency. In this article, we provide an overview of the current legislation on MS level regarding off-label prescription in order to support EU regulatory discussions.

Methods: Relevant national legislation regarding off-label prescription from MS was identified by distributing a questionnaire to EMACOLEX. Case law was excluded. The identified *categorical elements* and prerequisites in the national legislation were then categorised. Subsequently, a comparison was made to the five Good Off-Label Use Practice (GOLUP) principles.

Results: Based on the obtained responses from 10 MS, we observed a large heterogeneity in the legislation of MS regarding off-label prescription. Five (out of 10) MS regulate off-label prescription explicitly and seven (out of 10) MS have prerequisites. One or more prerequisites per MS were reflected in the GOLUP principles as formulated in 2017.



© The Author(s) 2021. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



Conclusion: The main contribution of this work is to flag that off-label prescription actually needs to be well defined and understood before it can be appropriately taken into consideration in regulatory discussions. There is a heterogeneity in legislation regarding off-label prescription in the investigated MS, which may lead to different perspectives. A common understanding of the concept and more alignment in off-label prescription practices and their regulation at MS level may contribute to further regulatory discussions.

Keywords: Off-label prescription, national legislation, categorical elements in law, GOLUP principles

INTRODUCTION

Off-label use and prescription are often referred to in the context of different discussions related to medicine development, approval and use. Prescription is part of European health policies, but it falls within the responsibility of the Member States (MS)^[1]. Hence, how individual MS regulate off-label prescription is an internal matter of the MS^[2]. Additionally, based on different sources, the prevalence of off-label prescription is reported as being extremely variable.

Recent judgements of the Court of Justice of the European Union have triggered a discussion about off-label use of medicinal products and the extent to which these practices and data generated may be considered in the context of assessment of dossiers for approval of medicinal products^[3]. Several categories of medicines, including orphan medicinal products, medicines for paediatric use and medicines in oncology and the central nervous system, should be approved via the centralised procedure. This centralised authorisation procedure is covered by European Union (EU) legislation^[4]. The clinical experience with off-label prescription in the discussions related to approval of medicinal products can be different. For instance, according to the Orphan regulation, one criterion that needs to be fulfilled (if applicable) is “significant benefit”. That means that, in cases where other satisfactory methods exist for the same indication, the medicinal product applied should be shown to be of significant benefit for the patients affected by the same condition. When defining which medicinal products to include as a comparator for assessing significant benefit, off-label prescribed medicinal products should not be considered a satisfactory method of treatment^[5]. On the other hand, off-label use is widely considered when discussing medicinal products for paediatric patients^[6-8]. Moreover, off-label use can be the basis for well-established use procedures^[9]. Such a procedure can be started when an active substance of a medicinal product has been used for more than 10 years and its efficacy and safety have been well established, often based on results from the scientific literature^[9].

Related to the above, the aim of this research was to provide an overview of the current legislation concerning off-label prescription and use of medicinal products in the distinct MS of the EU. In our study, we used the following definition for off-label prescription: “prescription of medicinal products not in accordance with the Summary of Product Characteristics (SmPC) for which the medicinal product is authorised”. Since this study focused on the EU, only medicinal products that have been authorised for at least one indication by the European Commission or by a National Competent Authority were included. Consequently, the term (marketing) authorisation in this study refers to approval in the EU. This definition was also used in the study of Weda *et al.*^[10] (2017). Off-label prescription occurs when an authorised medicinal product is prescribed for a different patient group, another indication, via a different administration route or with a different frequency or altered dose than included in the SmPC of that authorised medicinal product^[11,12]. First, we identified the elements present in national legislations associated with off-label prescription. Subsequently, we made a classification based on the legislation in the MS, as well as assessed the content of the legislation in relation to the principles from the Declaration on Good Off-Label Use in Practice (GOLUP)^[13].

SOURCES AND METHODS

We prepared a questionnaire consisting of four open questions about national legislation regarding off-label prescription [[Supplementary Material 1](#)]. This questionnaire was distributed among legal experts of the European Medicines Agencies Cooperation on Legal Issues (EMACOLEX). EMACOLEX is mandated to enhance trust, knowledge and confidence between legal staff in order to legally assist the European Medicines Regulatory Network and the national medicines agencies^[14]. At least three email reminders were sent. Based on the EMACOLEX questionnaire, the national legislation references of the primary sources of national legislation - the laws in their original language - for each MS were identified. Subsequently, the acts and regulations that were indirectly or directly associated with off-label prescription were examined in English with the use of a translation tool, with exception of the Dutch legislation which was studied in the original language. Case law was excluded, because the legal status varies between the countries and in most MS it is published in the original language only. Despite the existing possibility for translation from the original language, we decided not to follow this approach as it is known that certain nuances can be lost in translation and hence lead to incorrect interpretation.

Identification of categorical elements in law from national legislation

The method for comparative legal research, as executed by Elkins *et al.*^[15] in 2009 and applied by Voermans^[16] in 2019, was used for the identification of elements in law that were associated with off-label prescription. The identified regulated subjects from the national legislation of MS were categorised into *categorical elements in law* and the frequency of each of these elements was counted [[Figure 1](#)].

Analysis of classification

First, based on the nature of the legislation, a classification was made between explicit and implicit regulation regarding off-label prescription. MS that make in their national legislation a distinction between non-authorised medicinal products (“use or prescription without marketing authorisation”) and authorised off-label medicinal products (“use or prescription outside the terms of the marketing authorisation”) were categorised to have explicit regulation. MS that did not make such distinction were classified as having implicit regulation. Since this study focused on the EU, “marketing authorisation” refers to authorisation by the EC or any of the national competent authorities.

Second, MS were classified based on the extent of regulation, based on two parameters: the number of regulations and the number of prerequisites. The number of regulations was defined by the number of distinct sections - an article of law in a certain act or code - that have a direct or indirect association with off-label prescription of medicinal products. The number of distinct subsections or sub-articles of regulations was not counted. The number of regulations which are related to off-label prescription shows to what extent a MS has made regulations about the topic. The number of prerequisites was defined by the number (between 0 and 14) of prerequisites for off-label prescription. Prior to the analysis of classification, prerequisites were identified from the *categorical elements* in legislation. The number of *prerequisites* is an indication of the level of granularity in which the topic of “off-label prescription” is addressed in a certain MS. The complete list of these prerequisites can be found in [Supplementary Material 2](#).

Analysis of content of legislation

To assess the content of legislation, the prerequisites for off-label prescription identified in the national legislation of MS were related to the five GOLUP principles [[Supplementary Material 3](#)]^[13]. The frequency of each prerequisite was counted. GOLUP aims to create a harmonised approach on how and when off-label prescription might take place in the EU^[13]. The five GOLUP principles are as follows:

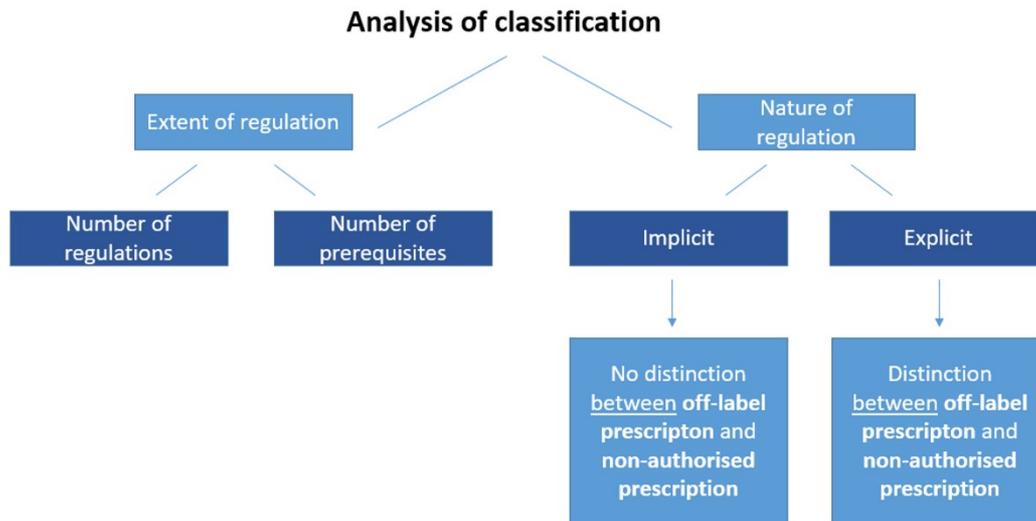


Figure 1. Overview analysis of classification.

1. “Presence of a medical therapeutic need based on a current examination of the patient by a suitably qualified health care professional”.
2. “Absence of authorised treatment and licensed alternatives tolerated by the patient or repeated treatment failure”.
3. “A documented review and critical appraisal of available scientific evidence favours off-label use to respond to the unmet medical need of the individual patient”.
4. “Patients (or their legal representative) must be given sufficient information about the medicines that are prescribed to allow them to make an informed decision”.
5. “Presence of established reporting routes for outcomes and adverse events linked to off-label use”^[13].

RESULTS

Responses were received from 10 EU MS and 3 EEA countries [Figure 2]. Since this research was initiated to inform EU regulatory discussions, the information from the EEA countries was appreciated but not included in the final analysis. In total, 24 *categorical elements* in legislation were identified. The full list of *categorical elements* can be found in [Supplementary Material 4](#). Figure 3 displays the elements that were found in the legislation of two or more MS. In five out of 10 MS, there was no definition or reference to off-label prescription in the national legislation, whereas, in the other five MS, a definition or reference to off-label prescription was present. In five MS, “informed patient consent” was found. *Categorical elements* such as the “professional standards of physicians”, “responsibility in case of off-label prescription” and “notification of a policy organ” were found in the lowest number of MS. In addition, “Distinction” (five MS) and “No distinction” (five MS), respectively, refer to whether there is a distinction in legislation between non-authorised medicinal products and off-label prescribed medicinal products or not. This in fact categorises a MS as having implicit or explicit legislation.

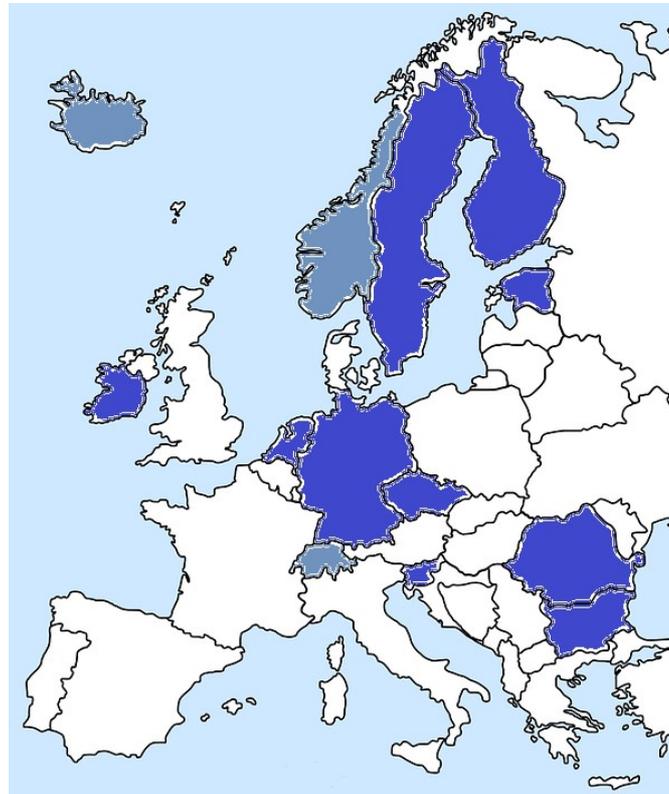


Figure 2. Responding countries. Light blue: EEA countries; dark blue: included MS for the research.

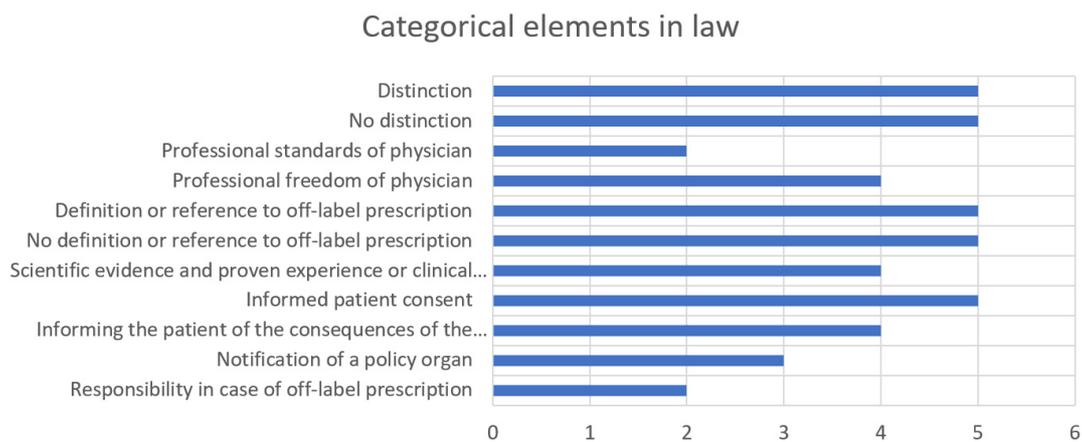


Figure 3. On the y-axis, the categorical elements that are present in at least two different MS are displayed. On the x-axis, the number of MS that have a certain categorical element are displayed. Categorical elements in law associated to off-label prescription. "Distinction" and "No distinction", respectively, refer to whether there is a distinction in legislation between non-authorized medicinal products and off-label prescribed medicinal products in a MS legislation. MS: Member States.

Classification of legislation associated with off-label prescription

Table 1 provides an overview of the extent to which off-label prescription is regulated. It includes the number of regulations, the number of prerequisites and the nature of regulation (explicit or implicit). The number of regulations that are associated to off-label prescription varies between one (Bulgaria, Czech Republic and Estonia) and five (Germany). Despite these differences in the extent of regulation, all MS have

Table 1. The extent and nature of regulations regarding off-label prescription in national legislation of MS

Member State	Extent of regulation		Nature of regulation
	Number of regulations	Number of prerequisites	
<i>Bulgaria</i>	1	8	Explicit
<i>Czech Republic</i>	1	3	Explicit
<i>Estonia</i>	1	4	Implicit
<i>Finland</i>	2	2	Implicit
<i>Germany</i>	5	0	Explicit
<i>Ireland</i>	2	2	Implicit
<i>The Netherlands</i>	4	4	Explicit
<i>Romania</i>	2	0	Implicit
<i>Slovenia</i>	2	0	Explicit
<i>Sweden</i>	2	2	Implicit

MS: Member States.

more general regulations, such as ethical or professional standards of the physician in general. Seven out of 10 MS have prerequisites for off-label prescription. Such prerequisites concern, e.g., “informed patient consent” or “notification of a policy organ”. Bulgaria has the most prerequisites for off-label prescription (8) and Ireland, Romania and Slovenia the fewest (0). However, the MS without prerequisites (Romania, Ireland and Slovenia) do have regulations that are related to the topic.

Lastly, five out of 10 MS were classified as having explicit regulation: Bulgaria, Czech Republic, Germany, The Netherlands and Slovenia. The other five MS were classified as having implicit regulation: Estonia, Finland, Ireland, Romania and Sweden. The legislation text of the MS with explicit regulation can be found in [Supplementary Material 5](#), and the number of regulations and national legislation references per Member State is presented in [Supplementary Material 6](#).

Content of legislation regarding off-label prescription

[Table 2](#) shows the 14 prerequisites for an off-label prescription of a medicinal product that have been identified in the law of the 10 MS. For each prerequisite, the relation to the GOLUP principles, the frequency and the MS in which the prerequisite has been identified are included. Except for “no payment of off-label treatment with public funds”, all identified prerequisites are related to the five principles stated in GOLUP Declaration^[13]. In fact, the prerequisite “no payment of off-label treatment with public funds” is related to the general aim of the GOLUP declaration.

The three most frequently applied GOLUP principles were: Principle 4 about informing the patient about the consequences of off-label prescription (nine times), Principle 5 regarding reporting outcomes and adverse events associated with off-label use (seven times) and Principle 3 concerning the scientific evidence for off-label use (five times). GOLUP Principle 2 about absence of alternative authorised treatments or repeated treatment failure was found only once. Bulgaria is the only MS that has included all five principles in their national legislation. However, all MS that have prerequisites for off-label prescription in their law (seven out of 10) have at least two prerequisites which are related to at least two different GOLUP principles, except for Germany that has two prerequisites that are related to the same GOLUP principle.

A comparison of the prerequisites in the different countries has shown different levels of similarities. For instance, Bulgaria and Sweden share three similar prerequisites (the highest “n” of similarities): “informed patient consent”, “scientific evidence” and “notification of a policy organ”. The last two are also found in the

Table 2. Prerequisites for off-label prescription, their frequencies and their relation to the GOLUP principles

Prerequisite	Frequency	Member State(s)	Relation to GOLUP principles
Absence of an alternative (on-label) treatment	1	Bulgaria	Principle 2
Scientific evidence and proven experience/clinical practice	4	Bulgaria, Finland, Czech Republic, Sweden	Principle 3
Assessment by special committee of physicians	1	Bulgaria	Principles 1 and 5
Prescription in hospital care	1	Bulgaria	Principle 1
Informed patient consent	5	Bulgaria, Germany, Estonia, The Netherlands, Sweden	Principle 4
Informing the patient of the consequences of the treatment	4	Czech Republic, Germany, Estonia, The Netherlands	Principle 4
Notification of a policy organ	3	Bulgaria, Czech Republic, Sweden	Principle 5
Monitoring and documenting the treatment	1	Bulgaria	Principle 5
No payment of the off-label treatment with public funds	1	Bulgaria	General aim of GOLUP
Conventional methods are not likely to be as effective	1	Estonia	Principle 1
Positive risk/benefit balance compared to on-label/conventional treatment	1	Estonia	Principle 1
Marking the prescription in case of deviation from the authorised dose	1	Finland	Principle 5
Developed standards or protocols	1	The Netherlands	Principle 3
Consultation between physician and pharmacist	1	The Netherlands	Principle 5

GOLUP: Good Off-Label Use Practice.

Czech Republic, Germany, Estonia and the Netherlands have two similar prerequisites: requirement for “informed patient consent” and “informing the patient about the consequences of the treatment”.

DISCUSSION

We studied the current legislation concerning off-label prescription and use of medicinal products in the distinct MS of the EU, which is of interest, as there is no EU legislation for off-label prescription. Hence, it is important to identify the exact nature of the national legislation in the different MS of the EU. Especially for marketing authorisation applications for medicinal products, it is currently not clear to what extent off-label use can be included in regulatory discussions at a European level at the different committees at the European Medicines Agency.

Our study is the first to investigate in detail the legislation of off-label prescription in the EU. We found that the national regulation for off-label prescription is heterogeneous in the different MS of the EU. Seven out of the 10 MS that responded to the EMACOLEX questionnaire have prerequisites for off-label prescription in their national legislation, and the number of regulations related to off-label prescription varied between one and five. Furthermore, five MS had explicit and five MS had implicit regulation for off-label prescription. It is noteworthy that several countries (Finland, Estonia and Sweden) did not define or refer to off-label prescription in their national legislation, but nevertheless they all had prerequisites for off-label prescription. However, the opposite was also observed. Germany refers to off-label prescription in national legislation, while the legislation only contains general prerequisites (i.e., informed patient consent) that do not apply exclusively to prescription of off-label products but to all medicinal products.

The lack of EU legislation and the current diversity of legislation regarding off-label prescription in the different MS leads to uncertainties. This issue was also flagged by Weda *et al.*^[10] in their study from 2017. They investigated 24 MS and found that 10 MS have regulations concerning off-label prescription of

medicinal products, while 14 MS do not have such regulations^[10].

In our study, we further analysed to what extent national legislations reflect the principles formulated in the GOLUP document. This document was signed in December 2017 by various European associations to summarise the main principles and ensure high standards of patient care^[13]. We identified that, in seven MS, the legislation and all 14 identified prerequisites are related to the GOLUP principles. The other three MS from the 10 responding countries do not have prerequisites at all and only in one MS (Bulgaria) the legislation contains all GOLUP principles. It seems that the GOLUP principles have been formulated based on the experience and elements from the legislation as reflected in the various MS.

This study has some limitations. The first is that the analysis is based on 10 of the 27 MS which responded to the questionnaire. Consequently, it is unclear whether the regulation in these MS is representative for the whole EU. However, based on these 10 countries, it can already be concluded that off-label prescription is very heterogeneously regulated. The second limitation is that only the legislation of MS was taken into account. Case law was excluded, for reasons already explained. It could however contribute to a more complete picture of the off-label prescription regulation throughout MS in the EU.

In conclusion, this review provides an overview of the current legislation regarding off-label prescription of medicinal products on MS level in the EU. The aim was to determine whether off-label prescription can be taken into consideration in regulatory discussions at EU level. We conclude that several steps are necessary before fully addressing this question. First, it is important to have one common understanding (a clear definition) of the concept of off-label prescription of medicinal products. Additionally, we checked to what extent national legislations' prerequisites have been reflected in the GOLUP principles of 2017. Despite the limitations of this study, we found that there is heterogeneity in legislation regarding off-label prescription in the investigated MS. Due to this, it may be expected that representatives of MS may have a different perspective regarding this concept.

Hence, the main contribution of this work is to flag that off-label prescription actually needs to be well defined and understood before taken into consideration in regulatory discussions. A common understanding of the concept and more alignment in off-label prescription practices and their regulation at MS level may contribute to further regulatory discussions.

DECLARATIONS

Acknowledgements

We thank the Members of the EMACOLEX for their participation in the survey. In addition, we appreciate the discussion meetings we had with Michael Klos (Leiden University, Faculty of Law, Department of Jurisprudence) and acknowledge him for his very useful feedback.

Authors' contributions

Collected the data and performed the primary analysis: Caminada R

Discussion and writing of the manuscript: Caminada R, Polano M, Pasmooij AMG, Stoyanova-Beninska V

Availability of data and materials

The data supporting this research can be found in the Supplementary Material.

Financial support and sponsorship

Not applicable.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2021.

REFERENCES

1. Article 168(1) and 168(2) Treaty on Functioning of the European Union. Available from: http://data.europa.eu/eli/treaty/tfeu_2008/art_168/oj [Last accessed on 22 Dec 2021].
2. Article 168(7) Treaty on Functioning of the European Union. Available from: http://data.europa.eu/eli/treaty/tfeu_2008/art_168/oj [Last accessed on 22 Dec 2021].
3. GCEU 23 September 2020, ECLI:EU:T:2020:444, Case T-549/19 (Medac Gesellschaft für klinische Spezialpräparate mbH v EC). Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A62019TJ0549> [Last accessed on 22 Dec 2021].
4. Regulation (EC) 726/2004. Available from: <http://data.europa.eu/eli/reg/2004/726/2019-03-30> [Last accessed on 22 Dec 2021].
5. Regulation (EC) 2000/141. In particular, article 3(1)(b) of the Regulation. Regulation (EC) No 141/2000 of the European parliament and of the council of 16 December 1999 on orphan medicinal products. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32000R0141> [Last accessed on 27 Dec 2021].
6. Recitals 2, 3, 4 of the preambles to Regulation (EC) 1901/2006. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:62009TJ0052&from=DA> [Last accessed on 22 Dec 2021].
7. Kimland E, Odland V. Off-label drug use in pediatric patients. *Clin Pharmacol Ther* 2012;91:796-801. DOI PubMed
8. Drenska M, Grigorova V, Elitova S, Naseva E, Getov I. The off-label use of medicines in pediatric outpatients in Bulgaria based on an analysis of their prescription data. *Drugs Ther Perspect* 2019;35:391-5. DOI
9. Article 10a Directive 2001/83/EC. DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67). Available from: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf [Last accessed on 22 Dec 2021].
10. Weda M, Hoebert J, Vervloet M, et al; Nivel; Dutch National Institute for Public Health and the Environment and European Public Health Alliance. Study on off-label use of medicinal products in the European Union. Available from: <https://www.nivel.nl/nl/publicatie/study-label-use-medicinal-products-european-union> [Last accessed on 22 Dec 2021].
11. Alenka BB, Vladimir B. The use of off-label drugs in medicine: ethical and legal issues. *Biomedicine and Surgery* 2017;1:84-7. DOI
12. European Medicines Agency. Off-label use. Available from: <https://www.ema.europa.eu/en/glossary/label-use>. Accessed 20 May 2021 [Last accessed on 22 Dec 2021].
13. Declaration on Good Off-Label Use Practice. Available from: https://www.braincouncil.eu/wp-content/uploads/2018/07/GOLUP_Declaration.pdf [Last accessed on 22 Dec 2021].
14. Heads of Medicines Agencies. European Medicines Agencies Co-operation of Legal and Legislative Issues (EMACOLEX). Available from: <https://www.hma.eu/482.html> [Last accessed on 22 Dec 2021].
15. Elkins Z, Ginsburg T, Melton J. The endurance of National Constitutions. New York: Cambridge University Press; 2019.
16. Voermans W. Het verhaal van de grondwet: zoeken naar wij. Amsterdam: Prometheus; 2019.