

Alternatives when an authorized medicinal product is not available

Francesca Selmin, Umberto M. Musazzi, Francesco Cilurzo, Paola Minghetti

Department of Pharmaceutical Sciences, Università degli Studi di Milano, Milan - Italy

ABSTRACT

The industrialization of medicinal products has permitted us to reach important results in terms of quality, efficacy, safety, and availability of drugs; however, not all the legitimate expectations of patients are met. When an authorized medicinal product is not available on the market, the physician can prescribe other pharmacological treatments in the following scenario: off-label prescriptions, extemporaneous preparations, compassionate use of medicinal products, and medicinal products authorized in foreign countries. The best solution among these alternatives should be evaluated case-by-case on the basis of good scientific evidence, expert medical judgement, and published literature, also keeping an eye on the availability, the cost, and the regulatory requirements at a national level.

Keywords: Compassionate use, Off-label use, Pharmaceutical compounding, Unlicensed medicinal product

Introduction

The enormous increase of knowledge in medicinal and pharmaceutical sciences determines the availability of important therapeutic aids for many pathologies. New drugs are often complex and potentially dangerous for humans. The experience with these drugs is responsible for the adoption of more stringent guidelines for the testing and approval of medicinal products by many regulatory agencies. A number of instruments have been put in place to guarantee a high level of protection for human health when a new medicinal product has to be granted the marketing authorization (MA). In other words, quality, efficacy, and safety are essential to assure that a medicinal product fulfils the legal requirements of an MA. The quality is mandatory to assure the safe and effective use of all the batches produced. The efficacy is related to the ability of medicinal products to treat a pathology for which the indication was proven in clinical trials involving target patients and well-defined procedures. On the other hand, the safety is strictly related to the risk/benefit ratio in relation to a specific disease. These concepts are susceptible to changes since an approved medicinal product can be withdrawn after postmarketing reports of new levels of evidence emerge.

Currently, in many countries, healthcare professionals are free to prescribe the most appropriate medicine for their patients among the industrial products available for that specific indication. However, authorized medicinal products do not cover all therapeutic needs of patients, despite the appearance of a number regulatory tools aimed to facilitate earlier access of patients to efficacious and safe medicines (1). Since 2012, in the USA, drugs that treat unmet medical needs – either by providing a therapy for an indication for which there are no other drugs or by improving available therapies – can obtain a fast-track designation and are eligible for more frequent meetings and written communication with the U.S. Food and Drug Administration (FDA) to discuss the drug's development program in addition to the rolling review of evidence. Breakthrough therapy designation is given to drugs that, based on preliminary clinical evidence, demonstrate substantial improvements over available therapies on clinically significant endpoints (2).

The European Medicines Agency (EMA) can grant a conditional MA (3), or an MA under exceptional circumstances (4), to allow patients access to medicines that could not be approved under a standard authorization since comprehensive data cannot be obtained. Conditional MA can be granted while the collection of comprehensive data is ongoing in order to address unmet medical needs in the case of seriously debilitating or life-threatening diseases, or emergencies, or orphan medicines. Moreover, the Committee for Medicinal Products for Human Use (CHMP) requires that the benefit-risk balance of the product is positive; that the applicant will be able to provide comprehensive data; and that the benefit to the public health of the medicinal product's immediate availability on the market outweighs the risks due to the need for further data. Once the applicant provides comprehensive data, it can become a "standard" MA (3).

Accepted: January 14, 2017

Published online: February 7, 2017

Corresponding author:

Paola Minghetti

Department of Pharmaceutical Sciences

Università degli Studi di Milano

via Giuseppe Colombo, 71

20133 Milano, Italy

paola.minghetti@unimi.it



MA, under exceptional circumstances, defines a type of marketing authorization granted to medicines where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical. This type of situation does not normally lead to the completion of a full dossier to become a “standard” MA (4).

These medicines are subject to specific postauthorization obligations and monitoring. Moreover, in March 2016, the EMA launched the Priority Medicine scheme “PRIME” to support the development of medicines that target these unmet medical needs, and to speed up the evaluation process so they can reach patients earlier (5).

However, rare disease drug development remains a challenge because there are too few patients to demonstrate efficacy and safety; they are often geographically dispersed and usually there is no other treatment available than the medicine under evaluation.

The situation is also very complex when medicinal products are intended for the pediatric population. It has been estimated that the availability of authorized and commercially available medicines for children varies between 48% and 54% of all approved medicines (6) and that up to 50% of pediatric patients received an unlicensed or off-label prescription (7). For instance, it is common practice to manually split tablets intended for adults in order to obtain lower doses, even if a significant proportion of quarters are not suitable in terms of weight and dose uniformity for administration in children with a weight and/or an active concentration outside of the required range (8). Moreover, the availability of medicines decreases according to age; neonates have the least appropriate medicines with respect to the information available (9). In addition to active ingredients, pharmaceutical excipients – in particular benzalkonium chloride, benzyl alcohol, dyes, propylene glycol and sulfites – constitute problems in infants because of the insufficient metabolic capacity in the first months of life (10).

Aiming to legitimate patients’ needs, the physician can prescribe pharmacological treatments other than that for which the MA has been granted, and if a medicine with an MA for the same indication is not available, there are these possibilities:

- off-label prescriptions;
- compounded medicinal products;
- compassionate use of medicinal products;
- prescription of medicinal products authorized in foreign countries.

Likewise, the physician should also consider the availability, costs, and local regulatory requirements if a community policy has not yet been established. Whether none of these alternatives are pursued, the physician should open a clinical trial which guarantees a higher level of safety, since the protocols require the approval of ethical commitments.

Off-label use

In order to obtain the EMA’s authorization for a particular use of a drug (or device), a substantial body of evidence as

proof is required regarding the efficacy, safety, and quality of that drug (or device) for specific clinical situations. In other words, only the competition of adequate and well-controlled clinical trials can document safety and efficacy for the new uses. When a drug is approved, indications and dosages are listed on the package insert, and only the risk–benefit ratio for those indications and dosages have been reviewed by the regulatory authorities.

Off-label use is the practice of prescribing a drug outside the terms of its official labelling since new uses for approved products are often discovered after marketing. It is worthy to note that the absence of labelling for a specific age group or for a specific disorder is not an implicit statement that the medicinal product is not efficacious or safe for that age or disorder. Rather, it only means that the evidence required to allow inclusion in the label has not been submitted to the regulatory authorities for review or has not met the regulatory standards of “substantial evidence” for approval. Indeed, due to the considerable time and effort required by clinical trials, applicants may not seek or obtain approval for new uses. For instance, the pharmaceutical companies may have no interest in pursuing any label extension since no increase of sale volumes occurs due to the limited number of patients. In other cases, the sponsor has carried out some research, but the new proposed use was found to be unsupported.

Off-label use may originate from a presumed drug class effect, an extension to milder forms of an approved indication, an extension to related conditions, an expansion to distinct conditions sharing a physiologic link, or an extension to conditions whose symptoms overlap with those of an approved indication. Numerous studies have revealed that off-label prescribing is a frequent occurrence in oncology due to the variety of cancer subtypes, the difficulty in performing clinical trials, the rapid diffusion of preliminary results, and the delayed approval of new drugs by the regulatory agencies (11).

Physicians’ freedom to prescribe drugs off-label carries important advantages for the individual patient: it permits innovations in clinical practice, particularly when approved treatments have failed; and it offers patients and physicians earlier access to drugs and the adoption of new practices based on emerging evidence. However, off-label use has potentially negative consequences; in fact, this practice does not always protect the safety of the patient because the level of evidence supporting off-label drug use is generally low (12–14). Therefore, physicians should prescribe off-label drugs only when there is a favorable risk–benefit ratio and no authorized medicines for the same indication are available. In any case, the Declaration of Helsinki recommends obtaining informed consent from the patient, including information on the rationale for the suggested treatment, the alternatives, the potential risks, and the expected benefits without exception. This requirement poses an ethical dilemma about how to protect the human dignity and autonomy of incapacitated patients. The FDA allows a waiver of consent (i.e., the exception of informed consent) in temporarily incapacitated adults only in emergency cases. The waiver of consent is based on the assumption that the patient would have given the informed consent and will do so after recovery (“Final Rule,” 1996). Therefore, if it is known that a patient would probably have not given consent, then he/she must not be included. In

contrast to the FDA, the European Council (2005) requires only a possible group benefit of studies in which the waiver of consent procedure should be applied. However, this protocol has not yet been ratified by many of the European authorities (15).

There are no differences in the case of the use of off-label drugs and devices: therapeutic decision making should always be guided by the best available evidence, and physicians must be willing to accept the consequences of their decisions. Obviously, the more scientifically sound the information supporting its use, the more confidently the physician and the patient can assess the possible value of the proposed unapproved treatment. As a consequence, the off-label use of a drug or a device should be based on sound scientific evidence, expert medical judgment, or published literature, whenever possible, provided that a medicine with an MA for the same indication is not available.

The question arises as to how the evidence-based use might be evaluated and the levels of evidence might be considered acceptable. For instance, cancer has been extensively characterized on the basis of genomics. The integration of genetic information with data on how the cancers respond to target-based therapy would optimize the cancer treatment. Recently, bioinformatics approaches have proposed to build a roadmap for matching the right drugs to the right patients (“precision medicine”) and, therefore, assist the off-label drug selection in oncology (16). Concerning the off-label prescription of biologics, it should preferably be “rational”; in other words, the prescription of an approved drug for another disease, which has proven to be safe and effective in a certain disease, should be based on shared signs and symptoms or knowledge on the pathophysiology of the disease (17, 18). On the other hand, for the pediatric population, gold standard clinical trials are often not available, so practitioners must rely on either less definitive information, such as expert opinion for the age group they are treating, or use evidence from a different population to guide the practice. The introduction of an electronic health record platform also should help to overcome these limitations, since an accurate documentation of the treatment indication at the time of prescribing may monitor the off-label use and pave the way for the enhanced postmarketing evaluation of drugs if they are linked to treatment outcomes (19, 20).

In the USA, the status of the “medically-accepted indication” of drugs and biological agents used off-label was determined by 5 designated compendia, namely a listing which summarizes evidence on the effectiveness of each drug or biologic, and provides information regarding clinical indications and proper dosages (21). A systematic review published in 2009 found that the quality of evidence cited in the compendia for off-label cancer drug usage was inconsistent, incomplete, and out-of-date (22). More recently, the current compendia-based approach for coverage decisions was still the subject of criticism since it lacked oversight and was not suitable for making safe recommendations or coverage decisions for cancer drugs (21). Moreover, multiple parties may have specific – and/or possibly conflicting – interests with respect to compendia development (23). Indeed, conflict of interest is an acknowledged, and largely unavoidable, factor in the development of drug compendia due to the nature of inputs to the process (data on drug effectiveness, safety,

toxicity, and use, which require selection and interpretation), the parties involved in the process (individuals with various relationships to the drug manufacturers), and outcomes of the process (listing in a compendium, which has financial implications) (23). In an attempt to keep patients and physicians informed, the FDA also permits scientific journals and conferences to present information about off-label uses for drugs. Although peer-reviewed literature serves as the gold standard for evidence-based medicine, the FDA’s review is not mandatory before disclosure (24). So, the distribution of selective publications, or the systematic manipulation of the literature from a self-interested source and the potential for undermining the new drug application review process, can occur (25). Moreover, the FDA guidance fails to recommend or require that manufacturers work toward key research that truly establishes the safety and efficacy of off-label use. However, the FDA has initiated a comprehensive review of its approach to off-label marketing and on November 2016, the agency convened a 2-day public hearing to address “its regulations and policies governing firms’ communications about unapproved uses of approved/cleared medical products” (26).

In contrast, the European Union (EU) does not allow widespread advertising of any off-label use by representatives of a pharmaceutical firm. Throughout the EU, there is not a common directive to control the “off-label” use, and each Member State can approve the procedure, guidance, and limit on its own. In the attempt to legitimate the patient’s need – despite the geographic borders – and avoid delaying the approval procedure, some European medical societies have suggested that lists of drugs accepted for selected off-label indications should be worked out in order to submit them to the common centralized procedure for approval of new drugs (27).

Compassionate use of medicinal products

The term “compassionate use” describes the use of an investigational new drug outside a clinical trial or a medicinal product that is the subject of an application for a centralized MA in the treatment of a chronically or seriously debilitating disease, or a life-threatening disease in the absence of valid therapeutic alternatives based on authorized products. The compassionate use of medicinal products assures the treatment availability for a group of patients excluded or not eligible, but only if the proposed conditions of use and target population overlapped those under clinical investigation.

There are different ways to make unapproved medicinal products available. In the internet age, patients are more aware of new treatments in the pipeline and they can try to gain access to unapproved medical drugs by making a personal request directly to the hospital (single-patient compassionate use). New unapproved therapies can be directly provided by the sponsoring company for patients who are not eligible for clinical trials (expanded access program) by way of exemption, or more often, it sets up a compassionate use program to allow many patients to get the drug outside the confines of a clinical trial. In all cases, the drug must be under study in a clinical trial (phase II and phase III already completed); data must show that the drug is likely to be effective and does not have unreasonable risks; and the drug company must be actively pursuing marketing approval.

At the EU level, compassionate use programs fall under Regulation (CE) No. 726/2004 of the European Parliament and of the Council of 31 March 2004, which introduces the frameworks for the scopes and general principles of compassionate use of medicinal products, defines the targeted human and veterinary patients and disease to be treated; namely, AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune disease and other immune dysfunctions, and viral disease (28). Article 83 expressly states that actuation of an efficacious compassionate use program remains a competence of a Member State. Indeed, when a Member State envisages the need to make a medicinal product available for compassionate use, the Competent Authority of that Member State must notify the EMA. The EMA/CHMP provides recommendations on the conditions of use, the conditions of distribution, and the patients targeted for compassionate use, after consultation with the applicant and the manufacturer. The up-to-date list of the opinions adopted on a public register is available on the EMA website (29).

Where a compassionate use program has been set-up in a Member State, the applicant should ensure that patients taking part in the program have access to the medicinal product during the period between the granting of the centralized MA and its placing in the market.

However, compassionate use is controversial because it is a double-edged sword. One of its benefits is that it offers desperate patients earlier access to drugs that might help them. However, with growing concerns over safety highlighted by recent pivotal trials in which drugs that were expected to help patients actually accelerated the disease, physicians are more reluctant to pursue this controversial practice (30). Moreover, whereas efficacy data emerging from compassionate use are of little value to regulatory agencies because of the lack of a comparison group, the safety data are viewed in exactly the same way as safety data from clinical trials. Hence, the emerging of unexpected adverse reactions could complicate the road to approval and, therefore, act as a disincentive for companies to allow widespread compassionate use of a drug.

Prescription of medicinal products authorized in foreign countries

The EU allows the free circulation of those human medicinal products granted by the centralized MA, the use of which is compulsory to new chemical entities to treat the HIV or AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, viral diseases, advanced-therapy medicines, and biotechnology products. It is optional for other medicines containing new active substances for indications other than those stated above that are a significant therapeutic, scientific, or technical innovation; whose authorization would be in the interest of public or animal health at the EU level. However, the majority of MA are still issued by national competent authorities through the mutual recognition procedure or the decentralized system. In the mutual-recognition procedure, an MA granted in a Member State can be recognized in other EU countries; in the decentralized system, a medicine that has not yet been

authorized in the EU can be simultaneously authorized in several EU Member States. Afterwards, companies can market the drug in all EU states, but they do not have to. For one reason or another, they may choose to market the drug in some countries but not in others.

In certain circumstances, a human medicine unlicensed in a single Member State can be imported and used to meet the special clinical needs of a patient that cannot be met by licensed medicines. The importation follows national procedures aimed at assessing the real need and the product's safety or quality.

Pharmaceutical compounding

Pharmaceutical preparation are defined in the European Pharmacopoeia monograph as "medicinal products generally consisting of active substances that may be combined with excipients, formulated into a dosage form suitable for the intended use, where necessary after reconstitution, presented in a suitable and appropriately labelled container" (31). A pharmacist can compound various ingredients to prepare suitable medicines when the proper commercial form or dosage is not available, or there is no MA, or the product license is used outside of their terms. In other words, pharmaceutical preparations from several procedures are justified only by the requirement to meet the special needs of individual patients that cannot be met by the pharmaceutical industry. Moreover, in special populations (i.e., pediatrics, geriatrics, patients with allergies), commercially available products need to be reformulated or made from different excipients to comply with specific medical or patient needs. Compounding also plays a fundamental role in the preparation of orphan drugs, drugs with stability issues, and medications awaiting MA (32).

The safety and effectiveness of a drug product depends on the potency, purity, and quality of ingredients, which, in turn, can be affected by how the drug is compounded. Risks in compounding include using incorrect formulae and calculations, selecting incorrect ingredients, using incorrect quantities, and producing unstable products (33, 34). The level of risk, could be minimized by improving the prescriber's knowledge of pharmacological and therapeutic activity and the pharmacist's knowledge of compounding, by validating the procedures and requirements, and also by applying appropriate regulations. The last of these is currently the most critical point as the definition and regulation of pharmaceutical compounding are not harmonized in all European countries, and, even though there are some common definitions, the regulation generally falls under the local competencies of the national jurisdictions. As an example, the British National Formulary for Children is the UK standard reference for pediatric prescriptions, which also lists numerous formulae to be selected on the basis of the child's age.

In 2011, the Committee of Ministers of the Council of Europe adopted a Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients (34). They aimed to avoid the quality and safety gaps between medicinal products prepared in pharmacies and in the industry, and to harmonize the quality and safety assurance and the standards for compounded medicinal products among the European countries.

The Resolution underlines the responsibility of all health care professionals in pharmaceutical preparations. Moreover, it recognizes the added value of these preparations if they address the unmet needs due to medical, pharmaceutical, or personal reasons of a specific patient or patient group. Finally, the pharmacist is required to assess the risk of an extemporaneous preparation, taking into consideration the dosage form and administration route, the amount prepared, the pharmacological effect of the medicinal product for the envisaged route of administration, the therapeutic window, the type of preparation process, and if the preparation is intended for internal or external supply.

Conclusion

To legitimize the patient's right to be treated when the suitable licenced medical product is not available or cannot be prescribed, the following strategies can be pursued: (i) off-label prescriptions; (ii) compounded medicinal products; (iii) compassionate use of medicinal products; and (iv) the prescription of medicinal products authorized in foreign countries. The optimal solution should be evaluated case-by-case on the basis of good scientific evidence, expert medical judgement, and published literature, also considering the availability, the cost, and the regulatory requirements at a national level. Although a watchful eye should be always given to safeguard patients' rights and health, and to evaluate the appropriateness of medical prescriptions, the public administration should also consider new strategies. For instance, taking advantage of the health record platform, the agencies should develop a program for an undated inventory of off-label medications, after having defined a common ground of safety and efficacy. The formation of networking among the European Member States is highly auspicious in order to avoid the duplication of clinical trials and to spread the collected data, above all in the case of orphan pathologies. Based on these results, decisional trees also could be provided to medicinal health care professionals to select the most appropriate therapy for a pathology. In the prospect to lay the fundamentals of common knowledge of this topic, monographies also should be compiled. Once again, the most important issue is to define the level of evidence-based results which can be considered acceptable and who should the responsible for such an evaluation.

Disclosures

Financial support: No grants or funding have been received for this study.

Conflict of interest: None of the authors has a financial interest related to this study to disclose.

References

1. Leyens L, Richer É, Melien Ø, Ballensiefen W, Brand A. Available tools to facilitate early patient access to medicines in the eu and the usa: analysis of conditional approvals and the implications for personalized medicine. *Public Health Genomics*. 2015;18(5):249-259.
2. US Food and Drug Administration. Safety and Innovation Act. <http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCA/Act/FDASIA/ucm341027.htm>. Accessed January 18, 2017.
3. European Medicines Agency. Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorization for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500202774.pdf. Accessed January 21, 2017.
4. European Medicines Agency. Guideline on procedures for the granting of a marketing authorization under exceptional circumstances, pursuant to article 14 (8) of regulation (EC) No 726. EMEA/357981/2005. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004883.pdf. Accessed January 21, 2017.
5. European Medicines Agency. Priority medicine scheme "PRIME". http://www.ema.europa.eu/ema/index.jsp%3Fcurl%3Dpages/regulation/general/general_content_000660.jsp%26mid%3DW0b01ac058096f643. Accessed January 12, 2017.
6. Cuzzolin L, Zaccaron A, Fanos V. Unlicensed and off-label uses of drugs in paediatrics: a review of the literature. *Fundam Clin Pharmacol*. 2003;17(1):125-131.
7. Neubert A, Wong IC, Bonifazi A, et al. Defining off-label and unlicensed use of medicines for children: results of a Delphi survey. *Pharmacol Res*. 2008;58(5-6):316-322.
8. Casiraghi A, Musazzi UM, Franceschini I, et al. Is propranolol compounding from tablet safe for pediatric use? Results from an experimental test. *Minerva Pediatr*. 2014;66(5):355-362.
9. van Riet-Nales DA, de Jager KE, Schobben AF, Egberts TC, Rademaker CM. The availability and age-appropriateness of medicines authorized for children in The Netherlands. *Br J Clin Pharmacol*. 2011;72(3):465-473.
10. Breikreutz J, Boos J. Paediatric and geriatric drug delivery. *Expert Opin Drug Deliv*. 2007;4(1):37-45.
11. Lerosé R, Musto P, Aieta M, Papa C, Tartarone A. Off-label use of anti-cancer drugs between clinical practice and research: the Italian experience. *Eur J Clin Pharmacol*. 2012;68(5):505-512.
12. Chiu Y, Bero L, Hessol NA, Lexchin J, Harrington C. A literature review of clinical outcomes associated with antipsychotic medication use in North American nursing home residents. *Health Policy*. 2015;119(6):802-813.
13. Good CB, Gellad WF. Off-Label drug use and adverse drug events: turning up the heat on off-label prescribing. *JAMA Intern Med*. 2016;176(1):63-64.
14. Eguale T, Buckeridge DL, Verma A, et al. Association of off-label drug use and adverse drug events in an adult population. *JAMA Intern Med*. 2016;176(1):55-63.
15. Elger CE, Hoppe C. Informed consent in off-label use and incapacitated persons. *Epilepsia*. 2009;50(Suppl 12):79-80.
16. Cheng L, Schneider BP, Li L. A bioinformatics approach for precision medicine off-label drug selection among triple negative breast cancer patients. *J Am Med Inform Assoc*. 2016;23(4):741-749.
17. Musters A, Assaf A, Gerlag DM, Tak PP, Tas SW. Discovery of innovative therapies for rare immune-mediated inflammatory diseases via off-label prescription of biologics: the case of IL-6 receptor blockade in Castleman disease. *Front Immunol*. 2015;6:625-630.
18. Baeten D, van Hagen PM. Use of TNF blockers and other targeted therapies in rare refractory immune-mediated inflammatory diseases: evidence-based or rational? *Ann Rheum Dis*. 2010;69(12):2067-2073.
19. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med*. 2006;166(9):1021-1026.



20. Eguale T, Verma A, Tamblyn R. In defense of off-label prescribing — reply. *JAMA Intern Med.* 2016;176(6):861-862.
21. Green AK, Wood WA, Basch EM. Time to reassess the cancer compendia for off-label drug coverage in oncology. *JAMA.* 2016;316(15):1541-1542.
22. Abernethy AP, Raman G, Balk EM, et al. Systematic review: reliability of compendia methods for off-label oncology indications. *Ann Intern Med.* 2009;150(5):336-343.
23. White Paper. Potential conflict of interest in the production of drug compendia. McKinney R, Abernethy AP, Matchar DB, et al. Rockville (MD): Agency for Healthcare Research and Quality (US); 2009 Apr 27. <https://www.ncbi.nlm.nih.gov/books/NBK253242/>. Accessed January 18, 2017.
24. Dresser R, Frader J. Off-label prescribing: a call for heightened professional and government oversight. *J Law Med Ethics.* 2009;37(3):476-486, 396.
25. Mello MM, Studdert DM, Brennan TA. Shifting terrain in the regulation of off-label promotion of pharmaceuticals. *N Engl J Med.* 2009;360(15):1557-1566.
26. Federal Register. Manufacturer communications regarding unapproved uses of approved or cleared medical products. Public hearing; request for comments. 81 Fed Reg 60299. September 1, 2016. <https://www.federalregister.gov/documents/2016/09/01/2016-21062/manufacture-communications-regarding-unapproved-uses-of-approved-or-cleared-medical-products-public>. Accessed January 09, 2017.
27. Casali PG; Executive Committee of ESMO. The off-label use of drugs in oncology: a position paper by the European Society for Medical Oncology (ESMO). *Ann Oncol.* 2007;18(12):1923-1925.
28. Regulation (CE) No 726/2004 of the European Parliament and of the Council of 31 March 2004. http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf. Accessed January 18, 2017.
29. European Medicines Agency. Compassionate use programs http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp. Accessed January 12, 2017.
30. Ross E. Unapproved drug use: compassionate or cause for concern? *Lancet Neurol.* 2009;8(2):136-137.
31. Pharmaceutical preparations European Pharmacopoeia 9th ed., 9.0 Supplement (2017). <https://www.scribd.com/doc/38363641/European-Pharmacopoeia-7-0-2011>. Accessed January 18, 2017.
32. Minghetti P, Pantano D, Gennari CG, Casiraghi A. Regulatory framework of pharmaceutical compounding and actual developments of legislation in Europe. *Health Policy.* 2014;117(3):328-333.
33. Gudeman J, Jozwiakowski M, Chollet J, Randell M. Potential risks of pharmacy compounding. *Drugs R D.* 2013;13(1):1-8.
34. Council of Europe. Resolution CM/ResAP. (2011)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients. Committee of Ministers (2011). https://www.edqm.eu/sites/default/files/resolution_cm_resap_2011_1.pdf. Accessed January 18, 2017.