Therapy Perspectives
For Rational Drug Use & Disease Management

Year XX, N. 14, October 2017

Considerations about generic substitution of orphan drugs for the treatment of patients affected by rare diseases

Antonello Di Paolo
Department of Clinical and Experimental Medicine, Section of Pharmacology, University of Pisa, Pisa, Italy

Springer Healthcare Communications

Therapy Perspectives

Year XX, N. 14, October 2017

CONSIDERATIONS ABOUT GENERIC SUBSTITUTION OF ORPHAN DRUGS FOR THE TREATMENT OF PATIENTS AFFECTED BY RARE DISEASES

ISSN 1974-6679
ISBN 978 88 6756 350 0

Springer Healthcare Communications

Via Decembrio, 28
20137 Milano

www.springerhealthcare.it

Therapy Perspectives. Registered in Milan - Registration n. 128 - 3/10/1997

Publishing Director: Giuliana Gerardo

Printed in October 2017 by Lazzati Industria Grafica S.r.l. - Casorate Sempione (VA)

Publication not for resale aimed at medical practitioners.

Publication made possible by an educational grant from Orphan Europe - Recordati Group

OMIITPB500005

Considerations about generic substitution of orphan drugs for the treatment of patients affected by rare diseases

Antonello Di Paolo
Department of Clinical and Experimental Medicine, Section of Pharmacology, University of Pisa, Pisa, Italy

Introduction

Rare diseases affect, by definition, few people. Treatment of rare diseases is challenging for a variety of reasons including poor understanding of disease biology, delayed diagnosis, and difficulties in conducting clinical trials [1]. In addition, the development of novel drugs for small patient populations may not be profitable for pharmaceutical companies. As a consequence, rare diseases are also known as "orphan diseases", a term that effectively conveys the absence of research and market interest. Thanks to the introduction worldwide of incentives encouraging the development of orphan drugs, the treatment of some rare diseases has considerably improved over the past three decades [2]. However, the majority of rare diseases remain without a specific therapy and, when available, treatments are often inaccessible to many patients [1]. The elevated cost of treatment is the most common criticism of current orphan drug legislations and an important cause of limited access to treatment [3].

As the period of patent protection and marketing exclusivity is currently expiring for several orphan drugs, less expensive generic versions of small-molecule orphan drugs are becoming available. This may help reduce the economic burden of rare diseases. The main objective of the present article is to discuss the advantages and the risks associated with generic substitution in rare diseases. Following a brief review of the current knowledge of rare diseases and the status of orphan drug development, the article will discuss current guidelines for the development of generic drugs, their limitations, and potential consequences of generic substitution in the setting of rare diseases.

Rare diseases are a heterogeneous group of disorders sharing important characteristics

There are currently several definitions of "rare disease" [4]. According to the US Food and Drug Administration (FDA), a disease is rare when it affects less than 200,000 individuals in the US, while the European Medicines Agency (EMA) uses the prevalence threshold of 1/2,000 individuals to define a disease as rare [4]. In recent years, particular attention has been given to ultra-rare diseases, the prevalence of which ranges from < 1/50,000 to < 1/2,000,000 individuals [5,6].

Rare diseases constitute a heterogeneous group that includes genetic diseases, rare cancers, infectious diseases, autoimmune diseases, and neurologic disorders [7]. It is estimated that there are between 5,000 and 8,000 rare diseases affecting approximately 6% to 8% of the world population [8]. Therefore, collectively the number of patients suffering from a rare disease is high.

Although rare diseases differ substantially in terms of etiology and clinical presentation, they have important features in common. Rare diseases are usually chronic and severely disabling with a negative impact on life expectancy, physical and mental abilities, and

quality of life [9]. A genetic origin has been identified in about 80% of rare diseases and disease onset during childhood is frequent [9,10]. Indeed, it is estimated that 75% of rare diseases affect children [10].

Orphan drug status and the development of drugs for rare diseases

The recognition by governments and regulatory authorities that patients with rare diseases have a right to treatment equal to that of patients with common diseases has led to the introduction worldwide of policies that encourage the research, development, and marketing of orphan drugs [2]. Without such incentives many drugs for rare disease would not be developed and authorized [4]. To qualify for the incentives, a new medication must obtain an orphan designation before the application for marketing authorization is submitted [2]. Criteria for the designation of orphan status vary among countries, as does the definition of rare disease [2,4].

Orphan drug legislations have no doubt contributed to the development of treatments for rare diseases in recent years, as highlighted by the substantial increase in the number of orphan drug designations and approvals following legislation enactment (***Figure 1***) [11]. Of note, most new molecular entities (NMEs) granted an orphan drug designation and approved by the FDA in the period 1983-2014 were for rare cancers (***Figure 2***) [7].

Despite the achievements of orphan drug legislations, several problems remain unresolved including: the elevated costs of rare disease treatment; delayed or no access to treatment for many patients; the lack of research and development programs focused on children; the inadequacy of current incentives for ultra-rare diseases; the lack of a clear and unique definition of rare disease leading, in some instances, to inappropriate orphan status designation [1,3,12,13].

The economic impact of orphan drugs is the most debated issue. A concern frequently raised is that the

Figure 1. Orphan drug designations released per year in the EU and US (Modified from [1])

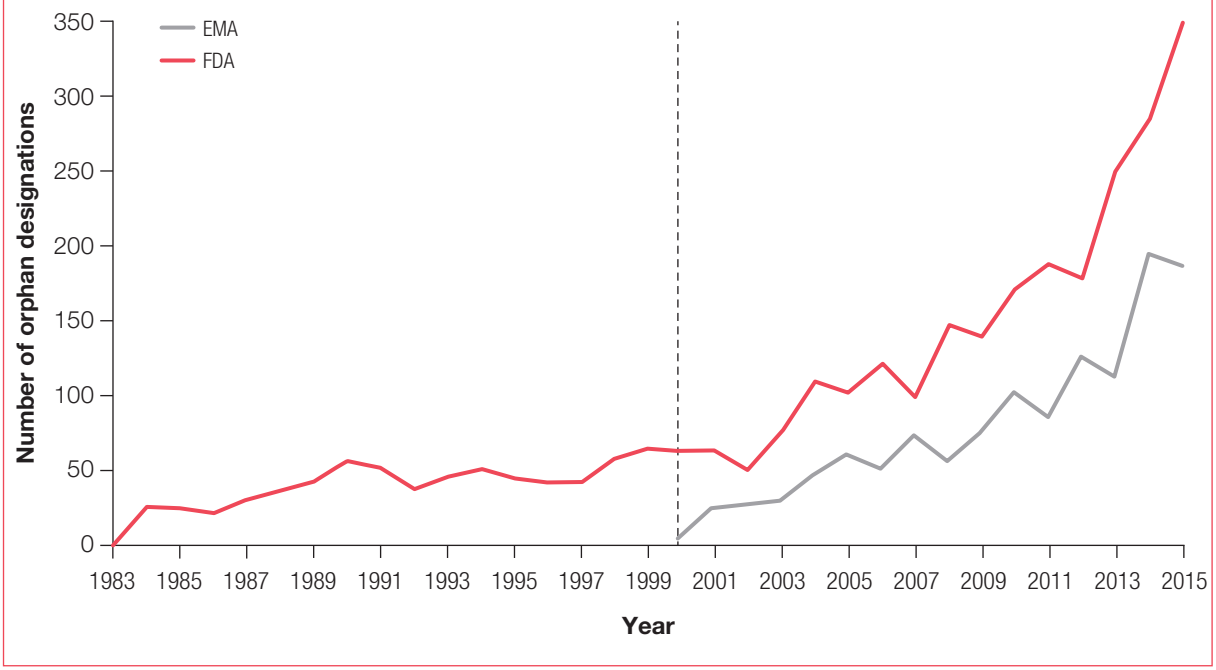
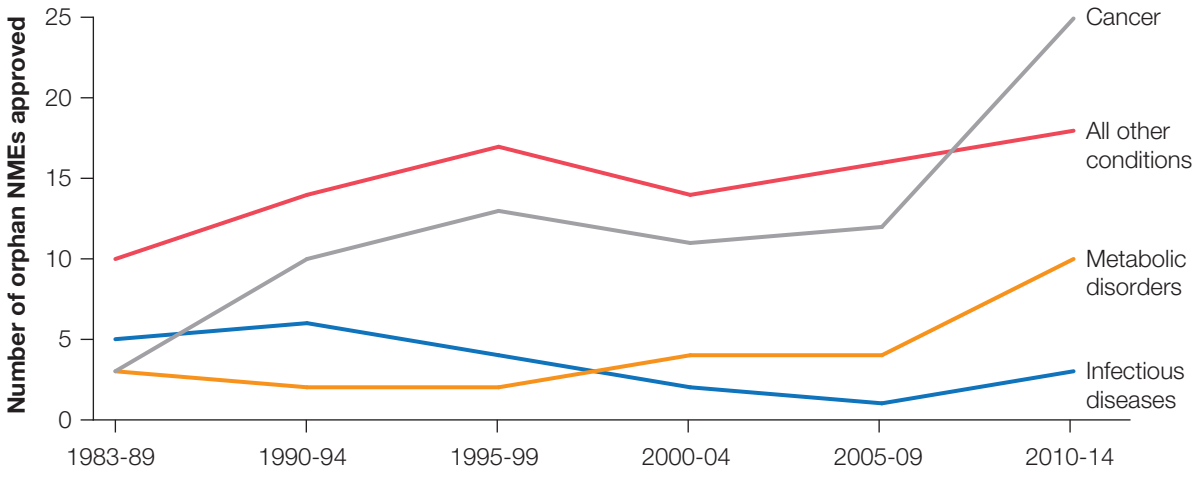


Figure 2. Orphan NMEs approved during 1983-2014, by therapeutic category (A) and number of NMEs by therapeutic category and time (B). Data from FDA. (Modified from [7])

A

Therapeutic category	Number of orphan NMEs		Examples of conditions treated
	All	With genetic origin	
Antidote	7	0	Lead poisoning, radiation poisoning
Cancer	74	0	Leukemia, mesothelioma, multiple myeloma, renal cell carcinoma
Cardiovascular diseases	8	0	Pulmonary arterial hypertension
Endocrine disorders	7	0	Cushing's disease, growth failure
Gastrointestinal disorders	7	1	Cholesterol biliary stones, short bowel syndrome
Hematologic disorders	12	3	Hereditary angioedema, essential thrombocythemia
Immunologic disorders	11	4	Castleman's disease, cryopyrin-associated periodic syndromes, organ transplant rejection
Infectious diseases	21	0	HIV, malaria, tuberculosis
Metabolic disorders	25	23	Gaucher disease, hyperphenylalaninemia, mucopolysaccharidosis 6, urea cycle disorders
Muscular or skeletal disorders	2	0	Dupuytren's contracture, Paget's disease
Neurologic disorders	20	1	Huntington's disease, multiple sclerosis, narcolepsy
Pulmonary diseases	9	2	Cystic fibrosis, idiopathic pulmonary fibrosis, respiratory distress syndrome
Renal or urinary disorders	6	1	Nephropathic cystinosis, secondary hyperparathyroidism

B



reimbursement of costly orphan drugs may occur at the expense of therapies for more common diseases [1]. It is also feared that the trend of increasing orphan drug approvals may have devastating effects on national healthcare systems [1]. Therefore, the replacement of orphan drugs with less expensive generic versions is understandably regarded as a way to solve at least one of the problems related to the treatment of rare diseases.

Limitations of current procedures for the approval of generic drugs

Generic drugs have become an important component of measures aimed at curbing healthcare costs worldwide. The main reason why generic drugs usually cost significantly less than their branded counterpart is because in order to obtain marketing authorization it is sufficient to demonstrate pharmaceutical equivalence (identical active substance) and bioequiva-

lence (comparable pharmacokinetics) between the generic and the reference product. Current pathways of generic drug approval do not require clinical trials. Bioequivalence is defined as the absence of a significant difference in the rate and extent to which the active ingredient in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions [14]. This means that the two compounds must show an overlapping bioavailability. The parameters used to measure bioavailability include the area under the plasma concentration-time curve (AUC) and the maximal plasma concentration (C_{max}). Studies evaluating these two parameters are performed in healthy volunteers. Average bioequivalence is established if the 90% confidence interval (CI) for the geometric mean of both the AUC and C_{max} for the generic product are within 80% and 125% of the corresponding parameters for the reference product [14,15].

Current bioequivalence criteria have been questioned by several authors [16,17]. A major limitation is the fact that bioequivalence studies are performed in small groups of healthy young adults and not in the target patient population, in which the response to drugs could differ significantly [16,18]. Physiologic changes associated with older age may affect drug absorption, distribution, metabolism, and excretion. As a consequence, differences in drug pharmacokinetics may exist in elderly patients that are undetectable in a healthy and younger population [16]. Children constitute another population not adequately addressed by current bioequivalence studies [19]. Human growth is not a linear process and, especially during the first decade of life, developmental changes in body composition and organ function are very dynamic leading to variable and unpredictable drug pharmacodynamics and pharmacokinetics [20]. There is a general consensus about the need to carefully monitor generic substitution in vulnerable patient populations [16,19]. With regard to the economic impact of complex generic substitutions, several authors have pointed out that the savings associated with the use of generic drugs may be nullified by increased costs associated with patient monitoring and management of adverse events [19,21].

Finally, certain drugs, for example those with a narrow therapeutic index, or a highly variable pharmacokinetic profile, may require more stringent and/or specific bioequivalence standards and acceptance criteria [22]. Also, due to the variability in pharmaceutical technologies, products containing the same active ingredient are rarely perfectly identical. Differences in excipients, particle size, salt form, and other aspects of product preparation have been shown to influence pharmacokinetic parameters, as well as the toxicity and tolerability profile [23,24].

Evidence of problematic generic substitution

Generic substitution is defined as the replacement of a prescribed branded drug by a generic drug that has the same active substance. Very limited data is available on the impact of generic substitution in rare and ultra-rare diseases. By contrast, the literature about generic substitution in more common diseases is extensive. Overall, for the majority of patients and medications, generic substitution has been shown to be an effective way to treat diseases at lower costs, without major problems. However, with certain classes of drugs including levothyroxine, immunosuppressants, antiepileptic drugs, antidepressants, and anti-cancer drugs, switching from the originator to the generic product has proven problematic and adverse clinical outcomes have been reported [16-18,21].

With regard to levothyroxine, a prospective randomized cross-over trial in 31 children with severe congenital hypothyroidism and low thyroid hormone reserve failed to confirm the bioequivalence to the reference product of a generic levothyroxine product previously considered by the FDA as bioequivalent

and interchangeable [25]. Significant differences in serum thyroid-stimulating hormone (TSH) concentrations were found after 8 weeks in patients receiving the branded versus the generic levothyroxine product [25]. Lack of efficacy in controlling TSH levels with levothyroxine generics has been reported also by the Medicines and Healthcare Products Regulatory Agency in the UK [17]. The general consensus in the field is that levothyroxine formulation substitution should be avoided in children with severe congenital hypothyroidism, particularly in those aged < 3 years because of the crucial role of TSH on brain development at this age [25].

Cyclosporine, a drug with a narrow therapeutic index, is frequently used as part of the maintenance immunosuppressive therapy in kidney and liver transplant patients. The introduction of generic cyclosporine formulations has raised concerns among physicians and patients because small changes in drug exposure have the potential to cause organ rejection when levels are low, or kidney toxicity when levels are high [17]. The generic SanCya was withdrawn from the market because it was found that its bioavailability was significantly different compared to the reference product when taken with apple juice, a common vehicle for oral administration in children [17]. Overall, the evidence as to whether the switch from branded cyclosporine to generic formulations will result in similar levels and outcomes in post-transplantation patients is conflicting [26]. Until conclusive data are available, current guidelines recommend to undertake generic substitution under close monitoring, especially in pediatric transplant recipients [26,27].

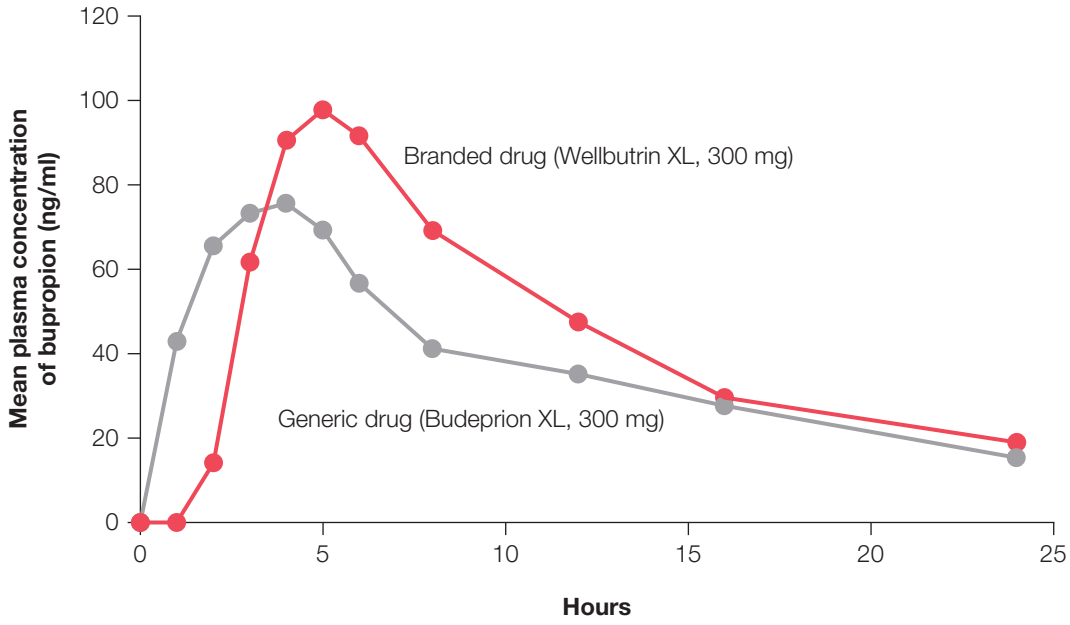
A comprehensive review of the literature documenting negative clinical and economic consequences of generic substitution on patient outcomes identified 30 articles, most of which were related to diseases of the nervous central system, in particular epilepsy [21]. The review highlighted three broad categories of potentially negative consequences: patient attitudes and adherence, clinical and safety outcomes, and cost and resource utilization. Several studies suggested that generic substitution might reduce patient adherence to medications, whereas other studies found that generic substitution was associated with worse clinical outcomes and more adverse events. Generic substitution was associated with savings, in some cases, but also with increased total healthcare costs due to increased visits to the physician or hospitalizations [21]. For example, a large study on the economic impact of generic antiepileptic drugs in the US found that the annual healthcare costs of patients treated with generics were 25% higher than for patients treated with branded products, despite the generics being less expensive [28].

Problems have been reported also with the switch to a generic version of Wellbutrin XL 300 mg (bupropion), a widely used antidepressant [29]. In 2006, the generic Budeprion XL 300 mg was found to be associated with adverse events (headaches, anxiety, depression, and sleeplessness) in patients treated for major depressive disorders who had switched to it from Wellbutrin XL 300 mg. Budeprion XL 300 mg had been approved based on the extrapolation of the results of bioequivalence studies conducted with 150-mg formulations. The report of adverse events with the generic prompted the FDA to conduct a head-to-head bioequivalence study, which failed to confirm the bioequivalence of the two products (***Figure 3***) and resulted in the withdrawal of generic bupropion [29].

Generics are increasingly used also in oncology. Generic imatinib, a tyrosine kinase inhibitor initially granted orphan drug status and approved in the US in 2001 for chronic myeloid leukemia, is now marketed in many countries. A recent article reviewing the literature about the toxicity and adverse events of the generic formulations of three classes of oncology drugs – docetaxel, cisplatin, and imatinib – compared with their reference drugs found that oncology generics used in the US and other developed coun-

Figure 3. Mean plasma concentration of bupropion [branded drug (Wellbutrin XL 300 mg) versus generic drug (Budeprion XL 300 mg)] over time in 24 healthy volunteers (Modified from [29])

The extent of bupropion absorption after the administration of the generic product (AUC) was 86% of the absorption with the branded product, but the corresponding 90% CI was 77% to 96%. In addition, the mean C_{max} observed after the administration of Budeprion XL 300 mg was only 75% of that observed after the administration of Wellbutrin XL 300 mg (90% CI, 65% to 87%). The time to C_{max} was also different for the two products, 4 hours for Budeprion and 5 hours for Wellbutrin. Such a difference had been observed also in the original bioequivalence study of the 150-mg products, but since the AUC and C_{max} values for the 150-mg products met the bioequivalence criteria, Budeprion XL 300 mg was approved.



tries are generally safe [30]. However, safety concerns have been raised for generic oncology products manufactured and used in developing countries, where manufacturing and supply chain regulations may be lax. According to the authors of this review, bioequivalence studies of oncology drugs with narrow therapeutic indices including tyrosine kinase inhibitors and cytotoxic agents are challenging and generic approval pathways should include product-specific requirements [30]. Post-marketing monitoring of generic oncology drugs is advisable [30].

Discussion and conclusions

Rare diseases are complex and often critical conditions for which timely treatment is crucial. Individuals affected by rare diseases belong to the category of fragile patients as they are, in many cases, very young and can present with multiple organ dysfunctions. Orphan drugs, in turn, are complex because they often exhibit a narrow therapeutic index and require extensive titration and carefully adjusted regimens. Based on these considerations, rare diseases clearly constitute a demanding therapeutic area in which generic substitution should be the result of an informed decisional process and may be contraindicated in some instances. By analogy with other complex therapeutic areas, generic substitution may result in differences with relevant consequences. In the setting of rare and ultra-rare diseases, where the therapeutic options are usually very limited, the switch to a generic version may be particularly hard to implement in those patients who have achieved

good disease control with the originator drug, as the switch may expose them to an unjustified risk of adverse outcomes.

The potential risk of increased adverse outcomes associated with generic substitution appears to be perceived also by patients, and this perception correlates with disease severity [16]. Also, patients with severe illnesses are less willing to switch to generics than other patients [31,32]. Patients are also reluctant to switch formulations when they feel comfortable with their current medication and when establishing the adequate therapeutic regimen was demanding [16]. Therefore, patient perception of treatment, which is known to influence compliance to it, should be also taken into account when considering generic substitution. Patients should be informed about generic substitution and its implementation should be a transparent process.

According to a recent opinion paper published by EURORDIS, current decision strategies in the field of rare diseases appear to focus excessively on economic aspects, while crucial issues like the improvement of patient outcomes and the production of additional clinical data seem less relevant [33]. The EURORDIS paper has also pointed out, based on the results of published pharmacoeconomic analyses, that the negative impact of increasing orphan drug use on national healthcare budgets may be overestimated, and that orphan drug expenditures account for a relatively small proportion of total pharmaceutical expenditures in several countries [33].

In conclusion, while the potential of orphan drug generics in improving the economic burden of rare diseases is recognized, caution is recommended in the switch from branded to generic drugs. Current bioequivalence assessments performed in healthy volunteers may be unable to capture differences between generic and originator drugs that may be clinically relevant in fragile patients with a severe or critical condition, as patients affected by a rare disease very often are. Therapeutic choices should never be made based exclusively on economic considerations. In rare and ultra-rare diseases, which are usually difficult to treat and have very few therapeutic options, this attitude may have even worse consequences than in more common and better-understood diseases.

References

1. Tambuyzer E. Rare diseases, orphan drugs and their regulation: questions and misconceptions. Nat Rev Drug Discov 2010;9:921-9
2. Gammie T, Lu CY, Babar Z U-D. Access to orphan drugs: a comprehensive review of legislations, regulations and policies in 35 countries. PLoS ONE 2015;10(10):e0140002
3. Rodriguez-Monguio R, Spargo T, Seoane-Vazquez E. Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients' health needs? Orphanet J Rare Dis 2017;12:1
4. Franco P. Orphan drug: the regulatory environment. Drug Discov Today 2013;18(3-4):163-72
5. NICE Citizens Council Report - Ultra orphan drugs. November 2004. https://www.nice.org.uk/Media/Default/Get-involved/Citizens-Council/Reports/CCReport04UltraOrphanDrugs.pdf. Last access: 21 September 2017
6. Hennekam RC. Care for patients with ultra-rare disorders. Eur J Med Genet 2011;54(3):220-4
7. Miller KL, Lanthier M. Trends in orphan new molecular entities, 1983-2014: half were first in class, and rare cancers were the most frequent targets. Health Aff (Millwood) 2016;35(3):464-70
8. Council of the European Union. Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02). Off J Eur Union. 2009;151:7-10. http://ec.europa.eu/chafea/documents/health/prague-rd-council-recommendation_en.pdf. Last access: 21 September 2017
9. Rare diseases: understanding this public health priority. EURORDIS, November 2005. http://www.eurordis.org/IMG/pdf/princeps_document-EN.pdf. Last access: 21 September 2017
10. What is a rare disease? EURORDIS, April 2007. http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf. Last access: 21 September 2017
11. Giannuzzi V, Conte R, Landi A, et al. Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: an increased

common effort is to be foreseen. Orphanet J Rare Dis 2017;12:64
12. Paediatric drugs and rare diseases. EURORDIS, March 2012. http://www.eurordis.org/content/paediatric-drugs-and-rare-diseases. Last access: 21 September 2017
13. Bourgeois FT, Hwang TJ. The Pediatric Research Equity Act moves into adolescence. JAMA 2017;317:259-60
14. Committee for Medicinal Products for Human Use (CHMP). Guideline on the investigation of bioequivalence. European Medicines Agency (EMA); 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Last access: 21 September 2017
15. FDA Fact Sheet. What's involved in reviewing and approving generic drug applications? https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/UCM510852.pdf. Last access: 21 September 2017
16. Meredith P. Bioequivalence and other unresolved issues in generic drug substitution. Clin Ther 2003;25(11):2875-90
17. Bate R, Mathur A, Lever HM, et at. Generic substitution, bioequivalence standards, and international oversight: complex issues facing the FDA. Trends Pharmacol Sci 2016;37(3):184-91
18. Crawford P, Feely M, Guberman A, Kramer G. Are there potential problems with generic substitution of antiepileptic drugs? A review of issues. Seizure 2006;15:165-76
19. Sherwin C. Issues associated with generic drugs used in children. GDUFA Regulatory Science Initiatives Public Meeting, May 20th 2016. https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM506188.pdf. Last access: 21 September 2017
20. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology – Drug disposition, action, and therapy in infants and children. New Engl J Med 2003;349:1157-67
21. Straka RJ, Keohane DJ, Liu LZ. Potential clinical and economic impact of switching branded medications to generics. Am J Ther 2017;24:e278-e289
22. Yu L, Jiang W, Zhang X, et al. Novel bioequivalence approach for narrow therapeutic index drugs. Clin Pharmacol Ther 2015;97(3):286-91
23. Verbeeck RK, Kanfer I, Walker RB. Generic substitution: the use of medicinal products containing different salts and implications for safety and efficacy. Eur J Pharm Sci 2006;28(1-2):1-6
24. Genazzani AA, Pattarino F. Difficulties in the production of identical drug products from a pharmaceutical technology viewpoint. Drugs R D 2008;9(2):65-72
25. Carswell JM, Gordon JH, Popovscky E, et al. Generic and brand-name L-thyroxine are not bioequivalent for children with severe congenital hypothyroidism. J Clin Endocrinol Metab 2013;98(2):610-7.
26. Singh AK, Narsipur SS. Cyclosporine: a commentary on brand versus generic formulation exchange. J Transplant 2011;2011:480642
27. Riva N, Guido PC, Ibanez J, et al. Therapeutic monitoring of pediatric renal transplant patients with conversion to generic cyclosporine. Int J Clin Pharm 2014;36(4):779-86.
28. Helmers SL, Paradis PE, Manjunath R, et al. Economic burden associated with the use of generic antiepileptic drugs in the United States. Epilepsy Behav 2010;18:437-44
29. Woodcock J, Khan M, Yu LX. Withdrawal of generic budeprion for nonbioequivalence. New Engl J Med 2012;367:2463-5
30. Yang YT, Nagai S, Chen BK, et al. Generic oncology drugs: are they all safe? Lancet Oncol 2016;17:e493-e501
31. Dohle S, Siegrist M. Cognitive and affective determinants of generic drug acceptance and use: cross-sectional and experimental findings. Health Psychol Behav Med 2013;1(1):5-14
32. Rathe JO. The effect of generic switching on concerns about medicine and non-persistence among Danish adults in a general practice setting. Dan Med J 2105;62(10):B5148
33. Breaking the access deadlock to leave no one behind. February 2017. A reflection paper by Eurordis and its members. http://www.eurordis.org/sites/default/files/reflexion-paper.pdf. Last access: 21 September 2017

EMEA-NM/HQ/PRO/OTH/ALL/Oct-17/240 – Cod: 1691