Title: Generic substitution of orphan drugs for the treatment of rare diseases: exploring the potential challenges

Author: Antonello Di Paolo[1], Elena Arrigoni[1]

Affiliation: [1]Department of Clinical and Experimental Medicine, Section of Pharmacology, University of Pisa, Pisa, Italy

Corresponding author: Antonello Di Paolo
Department of Clinical and Experimental Medicine, Section of Pharmacology, University of Pisa
Via Roma 55, 56126, Pisa, Italy
Phone: +39-050-2218755
Fax: +39-050-2218758
e-mail: antonello.dipaolo@med.unipi.it

ORCID: 0000-0002-2661-6183.

Running heading: Implications of generic substitution of orphan drugs

Word count

Submitted version: 4527

Revised version: 5192

Abstract

Generic drugs are important components of measures introduced by healthcare regulatory authorities to reduce treatment costs. In most patients and conditions the switch from a branded drug to its generic counterpart is performed with no major complications. However, evidence from complex diseases suggests that generic substitution requires careful evaluation in some settings and that current bioequivalence criteria may not always be adequate for establishing the interchangeability of branded and generic products. Rare diseases, also called orphan diseases, are a group of heterogeneous diseases that share important characteristics: in addition to their scarcity, most are severe, chronic, highly debilitating, and often present in early childhood. Finding a treatment for a rare disease is challenging. Thanks to incentives that encourage research and development programs in rare diseases, several orphan drugs are currently available. The elevated cost of orphan drugs is a highly debated issue and a cause of limited access to treatment for many patients. As patent protection and the exclusivity period of several orphan drugs will expire soon, generic versions of orphan drugs should reach the market shortly, with great expectations about their impact on the economic burden of rare diseases. However, consistent with other complex diseases, generic substitution may require thoughtful considerations and may be even contraindicated in some rare conditions. This article will provide an overview of rare disease characteristics, review reports of problematic generic substitution, and discuss why generic substitution of orphan drugs may be challenging and should be undertaken carefully in rare disease patients.

Key points

- Generic orphan drugs can contribute to reducing the costs of rare disease treatment but generic substitution is a complex process that should be implemented in a controlled and informed way
- The approach to generic substitution in rare diseases should go beyond the possible advantage offered by reduced drug acquisition costs, and should be based on a comprehensive, patient- and outcome-centered evaluation.

1. Introduction

Generic substitution refers to the replacement of a branded medical product by a generic version. As generic drugs are typically less expensive than the innovator product, their use is encouraged by health authorities across the world to reduce healthcare spending. In most patients and for the majority of drugs, generic substitution is undertaken successfully [1]. However, a few reports, especially from complex therapeutic areas, have described adverse outcomes including decreased treatment efficacy and tolerability, following the switch from a branded to a generic drug [2, 3]. Also, the adequacy of current procedures of generic approval has been called into question in some instances [4, 5, 2]. As a consequence, it is generally recognized that for some medications [i.e., narrow therapeutic index (NTI) drugs] in multisystemic diseases the switch to a generic formulation may require particular care to ensure that treatment efficacy and safety are maintained [2, 5, 4, 3].

Rare diseases, commonly referred to as 'orphan diseases' to indicate that they are neglected by research and development programs of pharmaceutical companies, affect by definition few people. However the number of rare diseases ranges from 5000 to 8000 and the population of individuals affected by a rare condition is collectively large and estimated to reach 30 million in the European Union (EU) [6-8]. Finding a treatment for rare diseases is a daunting task because of the scarcity of patients, insufficient knowledge of disease biology, lack of expertise in the medical community and difficulties in conducting clinical trials [9]. Therefore, rare diseases constitute a social and medical challenge [10].

The introduction of economic and regulatory incentives by governments and health authorities worldwide to encourage the development of treatments for rare diseases has resulted in the approval of an increasing number of so-called 'orphan drugs' [9, 11]. Orphan drugs are usually very expensive and the costs of rare disease treatments have raised concern [12, 9]. As the period of patent protection and marketing exclusivity is currently expiring for

several orphan drugs, less expensive generic versions are becoming available, which may result in decreased costs of rare disease treatment [13]. Generic versions of biologic drugs, called 'biosimilars' in the EU, will also become available soon for rare diseases. Unlike small-molecule generics, biosimilars are not identical to their innovator products and their approval procedure is complex [14-16]. As a result, the substitution potential of biosimilars is more limited compared with small-molecule generics and the economic advantages over innovator drugs are often modest [17].

Based on the reports of problematic generic substitution in other serious conditions, it cannot be ruled out that generic substitution may pose some problems also in rare diseases, owing to the complexity of most rare disorders (i.e., multisystemic involvement) and to the vulnerability of affected patients. The present article aims to explain why generic substitution should be undertaken thoughtfully in patients with rare diseases. This article will first focus on rare disease characteristics and the current status of orphan drug development; then current guidelines for generic drug approval, their limitations, and examples of therapeutic areas in which generic substitution has proven problematic will be briefly reviewed. Finally possible implications of generic substitution in rare diseases will be discussed.

2. Methods

A comprehensive search of the peer-reviewed literature was performed in PubMed using combinations of the terms 'rare disease', 'ultra-rare disease', 'orphan disease', 'orphan drug', 'generic drug', 'generic substitution' and 'bioequivalence'. Terms like 'children', 'pediatric patients', 'vulnerable patients', and 'fragile patients' were also included in the search because of the high prevalence of children in the population affected by rare diseases and treated with, or eligible to orphan drugs. Terms related to 'biosimilars' were also included in the search,

but strictly limited to orphan diseases in order to complete the analysis of literature. Retrieved articles were selected based on the title and abstract; for those considered of interest the full-text article was obtained. Additional publications were identified by screening the reference lists of the articles identified in PubMed. Web sites of international organizations of rare disease patients including EURORDIS (https://www.eurordis.org/about-eurordis), National Organization for Rare Disorders (NORD, https://rarediseases.org/), and Rare Disease UK (https://www.raredisease.org.uk/) were also searched with the above-mentioned terms.

3. Rare and ultra-rare diseases: definition and characteristics

The definition of rare disease varies across countries. In the USA, a disease is defined as rare when it affects less than 200,000 people in the country; in the EU, a rare disease is a life-threatening or chronically debilitating condition affecting less than 5 in 10,000 people [18]. There is currently no official definition of ultra-rare diseases. In the UK, the term describes conditions with a prevalence less than 1 in 50,000 people [19]. A prevalence of <10 in 1 million people has also been suggested for defining ultra-rare diseases [20, 21]. In ultra-rare diseases, drug research and development, as well as patient management, are even more difficult than in rare diseases [20-24]. Overall, the exact prevalence and the burden of rare diseases are unknown as epidemiology studies are lacking. Some rare diseases, for example mucopolysaccharidoses (a group of inherited metabolic diseases), have been more extensively investigated than others and attempts to improve epidemiologic data collection are beginning to emerge [25, 26].

Rare diseases constitute a heterogeneous group of disorders that can affect any organ. Examples of rare diseases include rare cancers, genetic disorders, neurological disorders, infectious diseases and autoimmune disorders [27]. Despite the great heterogeneity in terms

of etiology and clinical manifestations, rare diseases share important features (Table 1). Most rare diseases are chronic, severe to life-threatening and highly debilitating [28, 8].

Some orphan diseases are characterized by multisystemic involvement that could complicate the pharmacological management of patients. Leber's hereditary optic neuropaty (LHON) shows a progressive symptomatic worsening [29] associated with gastrointestinal dismotility, as it occurs in Friedreich's ataxia [30] and in endocrine diseases [31]. Those functional/organic alterations can affect drug disposition that may worsen the safety profile of narrow therapeutic index (NTI) drugs, as discussed below.

Availability of medicines and timely access to them are crucial to reduce morbidity and mortality [18]. Rare diseases have a negative impact on quality of life of affected people and their families who can suffer considerable emotional and financial stress [32, 33]. For most rare diseases (80%) a genetic component has been identified [8]. Many rare diseases can manifest in early childhood and often have fatal consequences [34]. It is estimated that approximately 70% of people affected by a rare disease are children [8, 28].

Beside the lack of specific therapies, a major problem in the treatment of rare diseases is late diagnosis both in children and adults. The average time from disease manifestation to diagnosis ranges from 5 to 30 years depending on the disease and this often leads to unnecessary medical interventions [9]. In newborns with inherited metabolic diseases, the lack of disease recognition and delayed access to treatment can have severe consequences, including mental retardation and death. The vital importance of the prompt recognition and treatment of rare diseases in newborns is highlighted also by the fact that increasingly expanded neonatal screening programs are mandatory in several countries worldwide. The Italian government, for example, has recently passed a law that makes newborn screening for over 40 inherited metabolic diseases mandatory (Legge 19 agosto 2016, n. 167) [35].

4. Development of orphan drugs

The recognition 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 to promote the research, development, and marketing of orphan drugs [18]. The incentives offered by such policies include several years of marketing exclusivity, tax credits for research costs, free scientific advice, fast track or priority review for marketing authorization, and pre-licensing access to orphan drugs [36]. To qualify for the incentives, a new medication must obtain an orphan designation before the application for marketing authorization is submitted [18]. Overall, criteria for the designation of orphan drug status take into account disease prevalence, as well as other disease characteristics and the expected commercial profitability of the drug, but differences exist among countries in the importance given to the various characteristics considered [36, 18]. In the USA, where the Orphan Drugs Act was passed in 1983, a drug is designated as orphan when it is intended to treat a disease that affects less than 200,000 persons in the USA, or affects more than 200,000 people and for which there is no reasonable expectation that the cost of developing and making it available will be recovered from sales in the USA [37, 38]. According to the orphan drug legislation enacted in the EU in 2000, a medicinal product is designated as orphan based on three criteria: the seriousness of the condition; the existence of alternative methods of diagnosis, prevention or treatment; either the rarity of the condition (affecting not more than 5 in 10,000 people in the EU) or insufficient returns when marketed in the EU [39].

Legislation related to orphan drugs has been very successful overall and not only improved the availability of treatment options for patients with rare diseases, but also promoted innovation [27]. Indeed, according to a recent analysis of orphan new molecular entities (NME) approved in the period 1983–2014 by the FDA (209 NME over a total of 429

approved orphan drugs), more than 50% of the orphan NME were first-in-class drugs [11]. By comparison, only 26% of non-orphan NME were classified as first-in-class drugs. Most approved orphan NME were for rare cancers. Of note, since 2011 the annual number of approved orphan drug has increased significantly, reflecting the greater interest in the development of drugs for rare diseases, as well as the progress in the identification of rare cancer subsets [11].

Despite the results obtained following initial orphan drug legislation, most rare diseases have no specific treatment. It is estimated that less than 10% of patients with rare diseases receive treatment today [27]. Ultra-rare diseases, in particular, may not be adequately addressed by current orphan drug legislations [40, 41, 21]. Other unmet needs of current orphan drugs policies include the lack research and development programs focused on children [42-47] and the inadequacy of pricing and reimbursement policies resulting in delayed access to orphan drugs [48-50].

The high cost of orphan drugs is perhaps the most debated issue [49, 47]. Although most EU healthcare systems cover treatment costs, the coverage might not be complete because of the high economic burden on patients [9]. Many have noted that reimbursement of costly orphan drugs may be at the expenses of medications needed to treat more common diseases, and that the increasing trend in the number of approved orphan drugs over the past few years might have negative effects on future national healthcare budgets [9, 51, 12].

5. Current regulations for the approval of generic drugs

Generic drugs are an important component of measures undertaken to reduce healthcare costs [17]. The main reason why the generics of small-molecule drugs usually cost less than their branded counterpart is because in order to obtain marketing authorization it is sufficient to

demonstrate pharmaceutical equivalence (identical active substance) and bioequivalence (comparable pharmacokinetics) between the generic and the innovator product. In contrast to the procedures involved in the approval of the innovator, evidence from large, costly clinical trials is not required [52, 53].

5.1 Bioequivalence studies

Bioequivalence testing is the cornerstone of USA and EU regulatory pathways leading to the approval of small-molecule generics. 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 (whereby a pharmaceutical alternative is a product containing the same active compound but differing in chemical form [salt, ester, etc.] of that compound or in the dosage form or strength) [53, 52]. This means that the bioavailability of the two products must be similar. 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 innovator product [52, 53].

With respect to differences in chemical drugs, biosimilars are characterized by higher molecular weight, complex chemical (and biochemical) structure and function [54] and they can differ from the originator in terms of post-translation modifications, purification processes, molecular targets (in the case of monoclonal antibodies [mAbs]) and immunogenicity. Facing those problems, regulatory agencies issued several guidelines for the production of biosimilars. In Europe, the comparability exercise includes three phases, during which the biosimilar is evaluated and compared with the originator for its quality and

similarity (phase I), pharmacokinetics and tolerability in preclinical studies (phase II) and its disposition, efficacy and tolerability in humans (phase III) [55]. However, the information about the pharmacokinetics and pharmacodynamics of an orphan drug is obtained "*in healthy volunteers and small numbers of patients with various conditions*" as occurred for miglustat [EMA guideline WC500207094]. From 2000 up to 2010, 38 out of 63 orphan drugs received EMA authorization after randomized controlled trials [56], with a global enrolment of less than 100 or 100-200 patients in one third or more than a half of these authorizations, respectively. The size of enrolled populations averaged 48 and 58 in interventional and observational studies, respectively [57]. These results strengthen the need for post-marketing trials and pharmacovigilance protocols [55].

5.2 Limitations of current procedures of generic approval

A number of authors have questioned the ability of currently used bioequivalence criteria to demonstrate the interchangeability of an innovator product and its generic counterpart, or the interchangeability of two generic products [2, 58, 5, 4, 3].

Another limitation is the fact that bioequivalence studies are performed in small groups of healthy young adults and not in the patient population for which the drug is approved.

As a result, bioequivalence data do not take into account possible variations associated with age, gender and disease [5, 4, 3], despite the high percentage of orphan disease patients in the tails of age distribution [59]. Indeed, physiological changes associated with older age, for example, may affect drug absorption, distribution, metabolism, and excretion. Consequently, differences in drug pharmacokinetics may exist in elderly patients that are undetectable in a healthy and younger population [4]. Children constitute another critical population, that is usually excluded from clinical trials [60]. During the first decade of life, developmental

changes in body composition and organ function are very dynamic and lead to non-linear and unpredictable drug pharmacodynamics and pharmacokinetics [61]. Based on the notion that pharmacokinetic parameters may vary between healthy individuals and certain patient subgroups, there is a general consensus about the need to carefully monitor generic substitution in critical patient populations such as children [4, 60]. The use of single-dose studies to predict the results of multiple-dose administrations is also regarded as a limitation of current bioequivalence studies [4]. Also, current guidelines do not require inactive ingredients in a generic formulation to be identical to those in the innovator formulation, although inactive ingredients can influence the response to treatment as well as the toxicity and tolerability profile [62, 4, 3, 63]. In this respect it should also be noted that, due to the variability in pharmaceutical technologies, products containing the same active ingredient are rarely perfectly identical [62]. Differences in various aspects of product preparation (excipients, particle size, salt form) are common and may have an impact on pharmacokinetic parameters as well as toxicity and tolerability profile [62]. Finally, drugs with a narrow therapeutic index (defined by the FDA as those drugs in which small differences in dose or blood concentration may lead to serious therapeutic failures and/or serious adverse drug reactions) [64], or drugs with a highly variable pharmacokinetic profile may require more stringent and/or specific bioequivalence standards and acceptance criteria than those currently indicated [4]. The need for different bioequivalent standards for drugs with a narrow therapeutic index is recognized by regulatory agencies: the EMA recommends more stringent limits (90% CI from 0.9 to 1.1) for these drugs, while the FDA continues to devote considerable effort to improve bioequivalence testing of critical-dose drugs [64, 52]. Some evidence suggests that the disease can significantly influence the pharmacokinetics of the active moiety. For example, the fluoroquinolone levofloxacin lost its bioequivalence in cystic fibrotic patients [65] hence increasing the risk of treatment failure.

The switch from one generic to another generic is poorly investigated and has also raised concerns [2, 5]. While the interchangeability of a branded and generic product is established by bioequivalence testing, the interchangeability of two generics is not directly proven but simply assumed. It is therefore possible that two generics are bioequivalent to the branded drug but not to each other [2, 5]. The use of different generic formulations may thus be an additional cause of variability in treatment outcomes. Of note, patients needing life-long treatment, including many of those affected by rare diseases, are more likely to experience switches from one generic to another due, for example, to shortage in the supply of a given formulation.

5.3 Problematic generic substitutions

Very limited data is currently available on the impact of generic substitution of orphan drugs for rare and ultra-rare diseases. In contrast, the literature on generic substitution for the treatment of more common conditions is extensive and includes reports of adverse outcomes associated with the switch from branded to generic products in a variety of therapeutic areas, especially when NTI drugs are involved [2, 5, 4, 3, 66]. Indeed, problems with generic substitution have been reported more consistently with certain drug classes including levothyroxine, post-transplantation immunosuppressants, anti-epileptic drugs, and antidepressants [67, 2, 68, 69, 3]. These reports have prompted additional bioequivalence studies, have often resulted in the withdrawal of the generic product, and have led several authors to recommend caution in the use of generics for certain conditions and patient populations.

With regard to levothyroxine, a prospective randomized cross-over trial in children with severe congenital hypothyroidism and low thyroid hormone reserve, showed that branded levothyroxine and an approved generic version were not bioequivalent [67]. The study found significant differences in serum thyroid-stimulating hormone (TSH) concentrations after 8

weeks in patients receiving the two levothyroxine formulations [67]. 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 [2]. As a consequence of these reports, levothyroxine generic substitution is not recommended in children with severe congenital hypothyroidism, particularly in those aged <3 years because of the crucial role of TSH on brain development in this age-group [67]. Interestingly, hypothyroidism, which is not a therapeutically complex condition, can be characterized by gastrointestinal dismotility [31] responsible for the alteration of levothyroxine absorption. Therefore, the accepted variability of a generic product in healthy volunteers could not be comparable to that observed in patients affected by an orphan disease with multisystemic involvement.

Other examples of multisystemic orphan disease and NTI drugs are available. Lymphangioleiomyomatosis affects several organs including liver parenchima and kidneys [70]. Sirolimus, an orally administered NTI drug, is an FDA-approved treatment of this rare disease, but it displays a "wide inter- and intrapatient variability in drug clearance" [71], hence changes in liver and kidney functions can alter its pharmacokinetics. Similar concerns have been raised by several researchers regarding the use of generic tacrolimus in transplanted patients [72, 73], and well-designed bioequivalence studies that include transplant patients are needed [74].

Gastrointestinal symptoms are not functional in neurofibromatosis type 1 (NF1), "but they may be part of the underlying NF1 disorder" [75], while the autosomal dominant optic atrophy may present gastrointestinal dismotility and constipation [30], implying possible effects on drug absorption.

Idebenone, which received the EMA orphan drug status for LHON, is activated by first-pass metabolism and displays a marked interindividual variability of drug pharmacokinetics [76] that might influence bioequivalence of generics in the presence of gastrointestinal

disturbances [30]. However, the high daily doses of idebenone registered for LHON treatment [77, 78] could spare patients from the risk of poor efficacy.

Generics are playing an increasingly important role in oncology. Imatinib, the first member of the tyrosine-kinase inhibitor class, was initially approved as an orphan drug for the treatment of chronic myeloid leukemia both in the USA (2001) and the EU (2005). Orphan drug status for the indication chronic myeloid leukemia was withdrawn in 2011 in the EU because the product no longer met the EMA criteria for orphan drug designation [79]. Several generic versions of imatinib are now available and marketed worldwide [80]. Case reports concerning the use of imatinib formulations authorized in developing and low-income countries have suggested differences in bioavailability and potency between branded and generic imatinib [80]. However, these results have not been confirmed with generic formulations approved by Western health authorities, which have proven to be effective overall [80, 81]. In line with these findings, 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 branded counterparts found that oncology generics used in the USA and other developed countries are generally safe, while safety concerns have been raised for generic oncology products manufactured and used in developing countries, where regulatory authorities have less experience in evaluating medicine quality [82]. According to the review, bioequivalence studies of oncology drugs with narrow therapeutic indices including tyrosine-kinase inhibitors and cytotoxic agents are challenging, so generic approval pathways should include product-specific requirements [82]. Furthermore, post-approval monitoring of generic oncology drugs is recommended.

A recent comprehensive review of the literature documented negative clinical and economic consequences of generic substitution on patient outcomes [3]. Noteworthy, three broad categories of potentially negative consequences of generic substitution may also apply to

orphan diseases: i) patients' attitudes and adherence, ii) clinical and safety outcomes, and iii) cost and resource utilization. Several studies suggested that generic substitution might reduce patient adherence to therapy due to confusion and concerns in patients who are stable on branded medications, whereas other studies found that generic substitution was associated with worse clinical outcomes and more adverse events.

Despite the evaluation process held by the EMA and FDA, concerns related to the administration of biosimilars are even greater than for chemical generics, because of the quality of the biosimilars and their immunogenicity. Indeed, the incidence of antidrug antibodies depends on both biosimilar characteristics (i.e., production and purification processes, storage and handling) and factors associated with the patient and his/her disease (i.e., route of administration, frequency and duration of treatment) [83-85]. Glycosylation is essential for the biological activity of erythropoietins (EPOs) [86], but the the pattern of glycosylation (number of residues and complexity of carbohydrate structures) depends on the cellular system used for the synthesis [87]. Indeed, EPO biosimilars can differ in glycosylation with respect their originators, and this was thought to be clinically irrelevant [88]; however, two EPO biosimilars presented a dissimilar glycosylation profile with respect to the originator and a different immunogenicity profile when tested in preclinical models [85]. Some authors believe that using an international nonproprietary name (INN) for these biosimilars will facilitate their use and postmarketing control [89]. Interestingly, recombinant human granulocyte colony-stimulating factor (rhG-CSF) can be used in its glycosylated (lenograstim) and non-glycosylated form (filgrastim) because glycosylation seems to be non essential for its biological activity, rather for proteolytic stability and prevention of aggregate formation [90]. For that reason, recent efforts have been focussed on the production of a fully synthetic aglycone G-CSF with predefined carbohydrate structures [91].

Another concern for biosimilars is the presence of impurities or different stabilizers that can increase immunogenicity [92]. Indeed, the presence of high concentrations of contaminating *E. coli* proteins in a biosimilar recombinant human growth hormone (rhGH) stimulated the production of anti-rhGH antibodies. Moreover, an interferon alpha2a pharmaceutical preparation that included human serum albumin (HSA) as stabilizer for room temperature storage was ten times more immunogenic than a HSA-free formulation stored in a refrigerator. Therefore, even in the case of storage and handling, biosimilars could differ from originators, positing additional questions about their safe use [83]. Several cases of pure red cell aplasia (PRCA) associated with EPO administration strengthened the issue of stabilizers. Although EPO was an originator, the substitution of HSA with polysorbate 80 (and probably the administration via subcutaneous injection, and insufficient attention to the cold chain and uncoated rubber stoppers within the syringe) could have increased the immunogenicity of the EPO itself [201926653]. Therefore, those events underline the need for particular attention to the pharmaceutical composition of medicine products based on therapeutic proteins and, in particular, of biosimilars. The extrapolation of clinical indications of a biosimilar is matter of concern for several authors, because differences in biological activity could not ensure the same degree of long-term efficacy and tolerability [89, 93].

Overall, the main issue for biosimilars is their therapeutic equivalence and interchangeability with respect to originators, because the process of bioequivalence is complex. In order to overcome this issue, FDA guidelines report the correct way in which interchangeability of biosimilars, with respect to originators, should be demonstrated in clinical trials [UCM537135]. Other authors are suggesting that real world data, pharmacovigilance protocols and prospective studies will also help in the growth of knowledge on biosimilars [55]. However, pharmacovigilance databases may be inadequate in rare diseases, thus fueling the search for new tools of analysis [94].

All of these factors, along with low numbers of treated patients, underline the difficulty in harvesting data regarding adverse drug events/adverse drug reactions (ADE/ADR) elicited by a switch from a branded to a generic drug. Furthermore, a chronic and worsening multisystemic orphan disease can mask ADE/ADR associated with the orphan drug. For example, idebenone can induce gastrointestinal toxicities [95] in LHON patients, in whom orphan disease can be characterised by severe symptoms and signs, which are chronic and can worsen over time [29]. However, pharmacokinetic and pharmacodynamic data, together with patient characteristics, suggest that some switches could result in an increased risk of ADE/ADR, as discussed in previous paragraphs.

6. Discussion and conclusions

Rare diseases are complex, chronic and severe conditions that require timely and, in most cases, life-long treatment. Individuals affected by rare diseases are fragile patients, typically children and very often neonates, infants or toddlers, who are treated based on the evidence extrapolated from studies performed in adults. The high cost of orphan drugs is one of the causes of limited access to treatment in rare diseases, especially for people living in countries where medication costs are not covered or are only partially reimbursed by healthcare systems or insurance plans. The introduction of generics is expected to improve access to treatment and reduce healthcare spending. However, based on the evidence demonstrating bioequivalence issues and adverse outcomes with generic medication in different populations, generic substitution may be problematic in rare diseases (Table 2).

Concerns about uncontrolled generic substitution – though related to biosimilars which are more complex than small-molecule generics – have been expressed by the US National Organization for Rare Disorders in a letter to the FDA urging the FDA to proceed carefully

with the development and approval of orphan biosimilars [96]. In particular, the letter has highlighted the need for transparency in the switch from the branded product to the generic version, and suggested the use of distinguished names for biosimilars to allow tracking of the exact treatment prescribed and ensure effective pharmacovigilance.

Although the high costs of orphan drugs remain an unresolved and intensely debated problem, cost is not the only cause of limited access to treatment. Other less recognized causes include the inadequacy and redundancy of pricing and reimbursement policies worldwide that clearly result in delayed and partial access to treatment [49, 50, 97]. According to general consensus among orphan drug experts, such policies urgently need revision, to improve their flexibility and the rapidity of decision-making. The difficulties of decision-making about orphan drugs largely come from the uncertainties surrounding the clinical benefits of the treatment. In this respect, it has been suggested that patients should be considered important sources of information that could contribute to reducing the uncertainties about orphan drugs [97].

Some information suggests that the focus on the high acquisition costs of orphan drugs may be excessive. An opinion paper recently published by EURORDIS has highlighted that the attention given to the costs of orphan drugs often overshadows other relevant and unresolved issues, which have a less prominent position in the public debate about the treatment of rare diseases [98]. Such issues include patient- and disease-centered problems like the improvement of patient outcome, the lack of clinical data, the under-representation of children, as well as insufficient disease knowledge for most rare and ultra-rare conditions. Regarding the real costs of rare disease treatments, evidence from studies conducted in Europe and elsewhere suggests that the impact of orphan drug costs on national healthcare budgets is relatively limited and usually below 6% of national budgets for medicines [99-103]. As noted in a recent paper that has investigated the problems associated with the access

to three expensive drugs used in pediatric nephrology, withholding a drug due to its cost is contradictory to an acceptable patient-doctor relationship, especially for those conditions with few treatment options [104]. However, under the increasing pressure to control healthcare costs, the access to an expensive drug is often limited by cost-saving policies. The use of generic treatment is mandatory in some therapeutic areas and may be extended, in an uncontrolled manner, to critical conditions that warrant more caution and thoughtfulness in treatment selection.

Patient needs should also be taken into account, and patients should be involved in decisions concerning generic substitution of orphan drugs. Patient perception of treatment, which is known to influence compliance, should also be addressed [105, 4, 106]. Of note, the perception of generics as being less effective and safe than their branded counterpart has been found to correlate with disease severity, which suggests that patients with rare and ultra-rare diseases may be more prone than others to refuse generic orphan drugs for fear of poor efficacy and safety. Evidence shows that patients are usually very reluctant to change treatment formulation if they are satisfied with their current medication [4]. Once a patient has found their optimal dose (which can take several attempts over a long period of time) they are unwilling to change treatment [4]. The negative perception of treatment can lead to poor adherence to treatment and also to nocebo effects [107]. A summary of the relationship between the various factors in rare diseases, its management and generic drugs is shown in Fig 1.

In conclusion, generic orphan drugs can contribute to reducing the costs of rare disease treatment and improving the access to treatment. In critical diseases and fragile patients, generic substitution is a complex process that should be implemented in a controlled and informed way, and should not be mandatory. The approach to generic substitution in rare

diseases should go beyond the possible advantage offered by reduced drug acquisition costs, and should be based on a comprehensive, patient- and outcome-centered evaluation.

Acknowledgments

The author thanks Lorenza Lanini, an independent medical writer acting on behalf of Springer Healthcare Communications, who drafted the outline and first draft of this manuscript, as well as Matt Weitz of Springer Healthcare Communications for English editing and formatting of the manuscript for submission. Mimi Chan, PhD, of Springer Healthcare Communications, assisted with English editing of post-submission revisions. This editorial support was funded by Orphan Europe – Recordati Group.

Compliance with ethical standards

Conflicts of interest: ADP acted as advisory board member for Novartis Farma SpA none to declare.

Funding: Orphan Europe – Recordati Group funded the assistance for medical writing.

References

1. US Food and Drug Administration (FDA). Facts about Generics. 2015: Available from http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/ucm167991.htm. Accessed 9 Sep 2017.
2. Bate R, Mathur A, Lever HM, Thakur D, Graedon J, Cooperman T et al. Generics substitution, bioequivalence standards, and international oversight: complex issues facing the FDA. Trends Pharmacol Sci. 2016;37:184-91. doi:10.1016/j.tips.2015.11.005.
3. Straka RJ, Keohane DJ, Liu LZ. Potential clinical and economic impact of switching branded medications to generics. Am J Ther. 2017;24:e278-e89. doi:10.1097/MJT.0000000000000282.
4. Meredith P. Bioequivalence and other unresolved issues in generic drug substitution. Clin Ther. 2003;25:2875-90.
5. 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. doi:10.1016/j.seizure.2005.12.010.
6. de Vrueh R, Baekelandt ERF, de Haan JMH. Updated on Background Paper 6.19: Rare Diseases. World Health Organisation. 2013: Available from http://www.who.int/medicines/areas/priority_medicines/BP6_19Rare.pdf. Accessed 9 Sep 2017.
7. European Organisation for Rare Diseases (EURORDIS). Rare diseases in numbers: Preliminary report from an on going bibliographic study initiated by Eurordis in partnership with Orphanet. Available from http://ec.europa.eu/health/archive/ph_threats/non_com/docs/rdnumbers.pdf. Accessed 9 Sep 2017.
8. European Organisation for Rare Diseases (EURORDIS). Rare diseases Europe: A factsheet. Available from https://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf. Accessed 9 Sep 2017.
9. Tambuyzer E. Rare diseases, orphan drugs and their regulation: questions and misconceptions. Nature Rev Drug Discov. 2010;9:921-9. doi:10.1038/nrd3275.
10. Schieppati A, Henter JI, Daina E, Aperia A. Why rare diseases are an important medical and social issue. Lancet. 2008;371:2039-41. doi:10.1016/S0140-6736(08)60872-7.
11. Miller KL, Lanthier M. Trends in orphan new molecular entities, 1983-2014: half were first in class, and rare cancers were the most frequent target. Health Aff. 2016;35:464-70. doi:10.1377/hlthaff.2015.0921.
12. 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. doi:10.1186/s13023-016-0551-7.
13. Onakpoya IJ, Spencer EA, Thompson MJ, Heneghan CJ. Effectiveness, safety and costs of orphan drugs: an evidence-based review. BMJ Open. 2015;5:e007199. doi:10.1136/bmjopen-2014-007199.
14. Chow SC, Wang J, Endrenyi L, Lachenbruch PA. Scientific considerations for assessing biosimilar products. Stat Med. 2013;32:370-81. doi:10.1002/sim.5571.
15. McKinnon R, Ward M. Safety considerations of biosimilars. Aust Prescr. 2016;39:188-9. doi:10.18773/austprescr.2016.084.
16. Stevenson JG. Clinical data and regulatory issues of biosimilar products. Am J Manag care. 2015;21(16 Suppl):s320-30.
17. Dylst P, Vulto A, Godman B, Simoens S. Generic medicines: solutions for a sustainable drug market? Appl Health Econ Health Policy. 2013;11:437-43. doi:10.1007/s40258-013-0043-z.

18. Gammie T, Lu CY, Babar ZU. Access to orphan drugs: a comprehensive review of legislations, regulations and policies in 35 countries. PloS one. 2015;10:e0140002. doi:10.1371/journal.pone.0140002.
19. National Institute for Clinical Excellence (NICE). NICE Citizens Council Report: Ultra orphan drugs. 2004: Available from https://www.nice.org.uk/Media/Default/Get-involved/Citizens-Council/Reports/CCReport04UltraOrphanDrugs.pdf. Accessed 9 Sep 2017.
20. Hennekam RC. Care for patients with ultra-rare disorders. Eur J Med Genet. 2011;54:220-4. doi:10.1016/j.ejmg.2010.12.001.
21. Putzeist M, Mantel-Teeuwisse AK, Wied CC, Hoes AW, Leufkens HG, de Vrueh RL. Drug development for exceptionally rare metabolic diseases: challenging but not impossible. Orphanet J Rare Dis. 2013;8:179. doi:10.1186/1750-1172-8-179.
22. Braun MM, Farag-El-Massah S, Xu K, Cote TR. Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. Nature Rev Drug Discov. 2010;9:519-22. doi:10.1038/nrd3160.
23. Harari S. Why we should care about ultra-rare disease. Eur Respir Rev. 2016;25:101-3. doi:10.1183/16000617.0017-2016.
24. Heemstra HE, van Weely S, Buller HA, Leufkens HG, de Vrueh RL. Translation of rare disease research into orphan drug development: disease matters. Drug Discov Today. 2009;14:1166-73. doi:10.1016/j.drudis.2009.09.008.
25. Khan SA, Peracha H, Ballhausen D, Wiesbauer A, Rohrbach M, Gautschi M et al. Epidemiology of mucopolysaccharidoses. Mol Genet Metab. 2017;121:227-40. doi:10.1016/j.ymgme.2017.05.016.
26. Leadley RM, Lang S, Misso K, Bekkering T, Ross J, Akiyama T et al. A systematic review of the prevalence of Morquio A syndrome: challenges for study reporting in rare diseases. Orphanet J Rare Dis. 2014;9:173. doi:10.1186/s13023-014-0173-x.
27. Melnikova I. Rare diseases and orphan drugs. Nature Rev Drug Discov. 2012;11:267-8. doi:10.1038/nrd3654.
28. European Organisation for Rare Diseases (EURORDIS). Rare diseases: Understanding this public health priority. 2005: Available from https://www.eurordis.org/IMG/pdf/princeps_document-EN.pdf. Accessed 9 Sep 2017.
29. Mancuso M, Orsucci D, Filosto M, Simoncini C, Siciliano G. Drugs and mitochondrial diseases: 40 queries and answers. Expert Opin Pharmacother. 2012;13:527-43. doi:10.1517/14656566.2012.657177.
30. Finsterer J, Frank M. Gastrointestinal manifestations of mitochondrial disorders: a systematic review. Therap Adv Gastroenterol. 2017;10:142-54. doi:10.1177/1756283X16666806.
31. Maser C, Toset A, Roman S. Gastrointestinal manifestations of endocrine disease. World J Gastroenterol. 2006;12:3174-9.
32. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. The supportive care needs of parents with a child with a rare disease: results of an online survey. BMC Fam Pract. 2016;17:88. doi:10.1186/s12875-016-0488-x.
33. Siddiq S, Wilson BJ, Graham ID, Lamoureux M, Khangura SD, Tingley K et al. Experiences of caregivers of children with inherited metabolic diseases: a qualitative study. Orphanet J Rare Dis. 2016;11:168. doi:10.1186/s13023-016-0548-2.
34. Thorat C, Xu K, Freeman SN, Bonnel RA, Joseph F, Phillips MI et al. What the Orphan Drug Act has done lately for children with rare diseases: a 10-year analysis. Pediatrics. 2012;129:516-21. doi:10.1542/peds.2011-1798.

35. Gazzetta Ufficiale. 2016: Available from http://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=20]. Accessed 9 Sep 2017.
36. Franco P. Orphan drugs: the regulatory environment. Drug Discov Today. 2013;18:163-72. doi:10.1016/j.drudis.2012.08.009.
37. 97th United States Congress. Orphan Drug Act of 1983: Public Law 97-414 – January 4, 1983. Available from https://history.nih.gov/research/downloads/pl97-414.pdf. Accessed 9 Sep 2017.
38. 98th United States Congress. Health Promotion and Disease Prevention Amendments of 1984: Public Law 98-551 – October 30, 1984. Available from https://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE--Pg2815.pdf. Accessed 9 Sep 017.
39. European Parliament and of the Council. Regulation (EC) No. 141/2000 on orphan medicinal products – 16 December 1999 Available from https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2000_141_cons-9-07/reg__141_cons-9-07_en.pdf. Accessed 9 Sep 17.
40. Clarke JT, Coyle D, Evans G, Martin J, Winquist E. Toward a functional definition of a "rare disease" for regulatory authorities and funding agencies. Value Health. 2014;17:757-61. doi:10.1016/j.jval.2014.08.2672.
41. Hughes DA, Tunnage B, Yeo ST. Drugs for exceptionally rare diseases: do they deserve special status for funding? QJM. 2005;98:829-36. doi:10.1093/qjmed/hci128.
42. European Organisation for Rare Diseases (EURORDIS). Medicines for children: better, more and faster. Eurordis position paper on the proposal for a regulation on medicinal products for paediatric use. 2005: Available from https://www.eurordis.org/IMG/pdf/eurordis__position__medicines_children_31jan05.pdf. Accessed 9 Sep 2017.
43. European Organisation for Rare Diseases (EURORDIS). Paediatric drugs and rare diseases. Available from https://www.eurordis.org/content/paediatric-drugs-and-rare-diseases. Accessed 9 Sep 2017.
44. Bourgeois FT, Hwang TJ. The Pediatric Research Equity Act moves into adolescence. JAMA. 2017;317:259-60. doi:10.1001/jama.2016.18131.
45. Connor E, Cure P. "Creating hope" and other incentives for drug development for children. Sci Transl Med. 2011;3:66cm1. doi:10.1126/scitranslmed.3001707.
46. Dooms M. From promising molecules to orphan drugs: Early clinical drug development. Intractable Rare Dis Res. 2017;6:29-34. doi:10.5582/irdr.2016.01094.
47. Hwang TJ, Bourgeois FT. New regulatory paradigms for innovative drugs to treat pediatric diseases. JAMA Pediatrics. 2014;168:879-80. doi:10.1001/jamapediatrics.2014.904.
48. Annemans L, Ayme S, Le Cam Y, Facey K, Gunther P, Nicod E et al. Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL). Orphanet J Rare Dis. 2017;12:50. doi:10.1186/s13023-017-0601-9.
49. Drummond M, Towse A. Orphan drugs policies: a suitable case for treatment. Eur J Health Econ. 2014;15:335-40. doi:10.1007/s10198-014-0560-1.
50. Feltmate K, Janiszewski PM, Gingerich S, Cloutier M. Delayed access to treatments for rare diseases: who's to blame? Respirology. 2015;20:361-9. doi:10.1111/resp.12498.
51. Kanters TA, Steenhoek A, Hakkaart L. Orphan drugs expenditure in the Netherlands in the period 2006-2012. Orphanet J Rare Dis. 2014;9:154. doi:10.1186/s13023-014-0154-0.
52. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP) guideline on the investigation of bioequivalence (Doc. Ref: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). 2010: Available from

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed 9 Sep 2017.
53. US Food and Drug Administration (FDA). FDA Fact Sheet: What's involved in reviewing and approving generic drug applications? . 2015: Available from https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/UCM510852.pdf. Accessed 9 Sep 2017.
54. Tsiftsoglou AS, Ruiz S, Schneider CK. Development and regulation of biosimilars: current status and future challenges. BioDrugs. 2013;27:203-11. doi:10.1007/s40259-013-0020-y.
55. Scavone C, Rafaniello C, Berrino L, Rossi F, Capuano A. Strengths, weaknesses and future challenges of biosimilars' development. An opinion on how to improve the knowledge and use of biosimilars in clinical practice. Pharmacol Res. 2017;126:138-42. doi:10.1016/j.phrs.2017.11.002.
56. Joppi R, Bertele V, Garattini S. Orphan drugs, orphan diseases. The first decade of orphan drug legislation in the EU. Eur J Clin Pharmacol. 2013;69:1009-24. doi:10.1007/s00228-012-1423-2.
57. Kanters TA, de Sonneville-Koedoot C, Redekop WK, Hakkaart L. Systematic review of available evidence on 11 high-priced inpatient orphan drugs. Orphanet J Rare Dis. 2013;8:124. doi:10.1186/1750-1172-8-124.
58. Cattaneo D, Andreoni M, Carosi G, Cauda R, Lazzarin A, Rizzardini G. Generic antiretrovirals for the treatment of HIV: a novel challenge for Western countries? Int J Clin Pharmacol Ther. 2017;55:381-93. doi:10.5414/CP202775.
59. de Barros CM, Papoila AL. Therapeutic profile of orphan medicines. Pharmacoepidemiol Drug Saf 2007;16:435-40. doi:10.1002/pds.1315.
60. Sherwin C. Issues associated with generic drugs used in children. GDUFA Regulatory Science Initiatives Public Meeting May 20th 2016. 2016: Available from https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM506188.pdf. Accessed 9 Sep 2017.
61. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. New Engl J Med. 2003;349:1157-67. doi:10.1056/NEJMra035092.
62. Genazzani AA, Pattarino F. Difficulties in the production of identical drug products from a pharmaceutical technology viewpoint. Drugs R D. 2008;9:65-72.
63. 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;28:1-6. doi:10.1016/j.ejps.2005.12.001.
64. Yu LX, Jiang W, Zhang X, Lionberger R, Makhlouf F, Schuirmann DJ et al. Novel bioequivalence approach for narrow therapeutic index drugs. Clin Pharmacol Ther. 2015;97:286-91. doi:10.1002/cpt.28.
65. Pai MP, Allen SE, Amsden GW. Altered steady state pharmacokinetics of levofloxacin in adult cystic fibrosis patients receiving calcium carbonate. J Cyst Fibros. 2006;5:153-7. doi:10.1016/j.jcf.2006.01.003.
66. Woodcock J, Khan M, Yu LX. Withdrawal of generic budeprion for nonbioequivalence. New Engl J Med. 2012;367:2463-5. doi:10.1056/NEJMp1212969.
67. Carswell JM, Gordon JH, Popovsky E, Hale A, Brown RS. Generic and brand-name L-thyroxine are not bioequivalent for children with severe congenital hypothyroidism. J Clin Endocrinol Metab. 2013;98:610-7. doi:10.1210/jc.2012-3125.
68. Riva N, Guido PC, Ibanez J, Licciardone N, Rousseau M, Mato G et al. Therapeutic monitoring of pediatric renal transplant patients with conversion to generic cyclosporin. Int J Clin Pharm. 2014;36:779-86. doi:10.1007/s11096-014-9959-0.

69. Singh AK, Narsipur SS. Cyclosporine: A commentary on brand versus generic formulation exchange. J Transplant. 2011;2011:480642. doi:10.1155/2011/480642.
70. Johnson SR, Taveira-DaSilva AM, Moss J. Lymphangioleiomyomatosis. Clin Chest Med. 2016;37:389-403. doi:10.1016/j.ccm.2016.04.002.
71. Mahalati K, Kahan BD. Clinical pharmacokinetics of sirolimus. Clin Pharmacokinet. 2001;40:573-85. doi:10.2165/00003088-200140080-00002.
72. Duong SQ, Lal AK, Joshi R, Feingold B, Venkataramanan R. Transition from brand to generic tacrolimus is associated with a decrease in trough blood concentration in pediatric heart transplant recipients. Pediatr Transplant. 2015;19:911-7. doi:10.1111/petr.12608.
73. Gonzalez F, Lopez R, Arriagada E, Carrasco R, Gallardo N, Lorca E. Switching stable kidney transplant recipients to a generic tacrolimus is feasible and safe, but it must be monitored. J Transplant. 2017;2017:5646858. doi:10.1155/2017/5646858.
74. Molnar AO, Fergusson D, Tsampalieros AK, Bennett A, Fergusson N, Ramsay T et al. Generic immunosuppression in solid organ transplantation: systematic review and meta-analysis. BMJ. 2015;350:h3163. doi:10.1136/bmj.h3163.
75. Ejerskov C, Krogh K, Ostergaard JR, Joensson I, Haagerup A. Gastrointestinal symptoms in children and adolescents with neurofibromatosis type 1. J Pediatr Gastroenterol Nutr. 2017. doi:10.1097/MPG.0000000000001860.
76. Becker C, Bray-French K, Drewe J. Pharmacokinetic evaluation of idebenone. Expert Opin Drug Metab Toxicol. 2010;6:1437-44. doi:10.1517/17425255.2010.530656.
77. Carelli V, Carbonelli M, de Coo IF, Kawasaki A, Klopstock T, Lagreze WA et al. International consensus statement on the clinical and therapeutic management of Leber hereditary optic neuropathy. J Neuroophthalmol. 2017;37:371-81. doi:10.1097/WNO.0000000000000570.
78. Lyseng-Williamson KA. Idebenone: a review in Leber's hereditary optic neuropathy. Drugs. 2016;76:805-13. doi:10.1007/s40265-016-0574-3.
79. European Medicines Agency (EMA). Committee for Orphan Medicinal Products. Public summary of opinion on orphan designation: Imatinib mesilate for treatment of chronic myeloid leukaemia (4 February 2015; EMA/COMP/10370/2003 Rev.5). 2015: Available from http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500006437.pdf. Accessed 9 Sep 2017.
80. Conti RM, Padula WV, Larson RA. Changing the cost of care for chronic myeloid leukemia: the availability of generic imatinib in the USA and the EU. Ann Hematol. 2015;94 Suppl 2:S249-57. doi:10.1007/s00277-015-2319-x.
81. de Lemos ML, Kyritsis V. Clinical efficacy of generic imatinib. J Oncol Pharm Pract. 2015;21:76-9. doi:10.1177/1078155214522143.
82. Yang YT, Nagai S, Chen BK, Qureshi ZP, Lebby AA, Kessler S et al. Generic oncology drugs: are they all safe? Lancet Oncol. 2016;17:e493-e501. doi:10.1016/S1470-2045(16)30384-9.
83. Jelkmann W. Biosimilar epoetins and other "follow-on" biologics: update on the European experiences. Am J Hematol. 2010;85:771-80. doi:10.1002/ajh.21805.
84. Praditpornsilpa K, Tiranathanagul K, Kupatawintu P, Jootar S, Intragumtornchai T, Tungsanga K et al. Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies. Kidney Int. 2011;80:88-92. doi:10.1038/ki.2011.68.
85. Tamilvanan S, Raja NL, Sa B, Basu SK. Clinical concerns of immunogenicity produced at cellular levels by biopharmaceuticals following their parenteral administration into human body. J Drug Target. 2010;18:489-98. doi:10.3109/10611861003649746.
86. Rademacher TW, Parekh RB, Dwek RA. Glycobiology. Annu Rev Biochem. 1988;57:785-838. doi:10.1146/annurev.bi.57.070188.004033.

87. Rush RS, Derby PL, Smith DM, Merry C, Rogers G, Rohde MF et al. Microheterogeneity of erythropoietin carbohydrate structure. Anal Chem. 1995;67:1442-52.
88. Schellekens H. The first biosimilar epoetin: but how similar is it? Clin J Am Soc Nephrol. 2008;3:174-8. doi:10.2215/CJN.04251007.
89. Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. Ann Oncol. 2008;19:411-9. doi:10.1093/annonc/mdm345.
90. Oh-eda M, Hasegawa M, Hattori K, Kuboniwa H, Kojima T, Orita T et al. O-linked sugar chain of human granulocyte colony-stimulating factor protects it against polymerization and denaturation allowing it to retain its biological activity. J Biol Chem. 1990;265:11432-5.
91. Roberts AG, Johnston EV, Shieh JH, Sondey JP, Hendrickson RC, Moore MA et al. Fully synthetic granulocyte colony-stimulating factor enabled by isonitrile-mediated coupling of large, side-chain-unprotected peptides. J Am Chem Soc. 2015;137:13167-75. doi:10.1021/jacs.5b08754.
92. Declerck PJ, Darendeliler F, Goth M, Kolouskova S, Micle I, Noordam C et al. Biosimilars: controversies as illustrated by rhGH. Curr Med Res Opin. 2010;26:1219-29. doi:10.1185/03007991003719642.
93. Lee H. Is extrapolation of the safety and efficacy data in one indication to another appropriate for biosimilars? AAPS J. 2014;16:22-6. doi:10.1208/s12248-013-9534-y.
94. Maro JC, Brown JS, Dal Pan GJ, Li L. Orphan therapies: making best use of postmarket data. J Gen Intern Med. 2014;29 Suppl 3:S745-51. doi:10.1007/s11606-014-2882-1.
95. Meier T, Buyse G. Idebenone: an emerging therapy for Friedreich ataxia. J Neurol. 2009;256 Suppl 1:25-30. doi:10.1007/s00415-009-1005-0.
96. Saltonstall PL, National Organization for Rare Disorders (NORD). Thoughtful biosimilars policy is best way to ensure optimum patient outcomes. 2014: Available from https://rarediseases.org/thoughtful-biosimilars-policy-is-best-way-to-ensure-optimum-patient-outcomes/. Accessed 9 Sep 2017.
97. Menon D, Stafinski T, Dunn A, Wong-Rieger D. Developing a patient-directed policy framework for managing orphan and ultra-orphan drugs throughout their lifecycle. Patient. 2015;8:103-17. doi:10.1007/s40271-014-0108-6.
98. European Organisation for Rare Diseases (EURORDIS). Breaking the access deadlock to leave no one behind: A reflection paper by EURORDIS and its members. 2017: Available from https://www.eurordis.org/sites/default/files/reflexion-paper.pdf. Accessed 9 Sep 2017.
99. Commission of the European Communities. Commission staff working document on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained. Document on the basis of Article 10 of Regulation (EC) No 141/2000 (SEC [2006] 832). 2006: Available from https://ec.europa.eu/health//sites/health/files/files/orphanmp/doc/orphan_en_06-2006_en.pdf. Accessed 9 Sep 17.
100. Divino V, DeKoven M, Kleinrock M, Wade RL, Kim T, Kaura S. Pharmaceutical expenditure on drugs for rare diseases in Canada: a historical (2007-13) and prospective (2014-18) MIDAS sales data analysis. Orphanet J Rare Dis. 2016;11:68. doi:10.1186/s13023-016-0450-y.
101. Hutchings A, Schey C, Dutton R, Achana F, Antonov K. Estimating the budget impact of orphan drugs in Sweden and France 2013-2020. Orphanet J Rare Dis. 2014;9:22. doi:10.1186/1750-1172-9-22.
102. Logviss K, Krievins D, Purvina S. Impact of orphan drugs on Latvian budget. Orphanet J Rare Dis. 2016;11:59. doi:10.1186/s13023-016-0434-y.
103. Schey C, Milanova T, Hutchings A. Estimating the budget impact of orphan medicines in Europe: 2010 - 2020. Orphanet J Rare Dis. 2011;6:62. doi:10.1186/1750-1172-6-62.

104. Karpman D, Hoglund P. Orphan drug policies and use in pediatric nephrology. Pediatr Nephrol. 2017;32:1-6. doi:10.1007/s00467-016-3520-4.
105. Dohle S, Siegrist M. Cognitive and affective determinants of generic drug acceptance and use: cross-sectional and experimental findings. Health Psychol Behav Med. 2013;1:5-14. doi:10.1080/21642850.2013.803828.
106. 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. 2015;62:B5148.
107. Weissenfeld J, Stock S, Lungen M, Gerber A. The nocebo effect: a reason for patients' non-adherence to generic substitution? Pharmazie. 2010;65:451-6.
108. Lichtman SM, Boparai MK. Anticancer drug therapy in the older cancer patient: pharmacology and polypharmacy. Curr Treat Options Oncol. 2008;9:191-203. doi:10.1007/s11864-008-0060-6.
109. Fernandez E, Perez R, Hernandez A, Tejada P, Arteta M, Ramos JT. Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. Pharmaceutics. 2011;3:53-72. doi:10.3390/pharmaceutics3010053.
110. Pisciotta L, Tozzi G, Travaglini L, Taurisano R, Lucchi T, Indolfi G et al. Molecular and clinical characterization of a series of patients with childhood-onset lysosomal acid lipase deficiency. Retrospective investigations, follow-up and detection of two novel LIPA pathogenic variants. Atherosclerosis. 2017;265:124-32. doi:10.1016/j.atherosclerosis.2017.08.021.
111. Paulino TL, Rafael MN, Hix S, Shigueoka DC, Ajzen SA, Kochi C et al. Is age a risk factor for liver disease and metabolic alterations in ataxia Telangiectasia patients? Orphanet J Rare Dis. 2017;12:136. doi:10.1186/s13023-017-0689-y.
112. El-Beshlawy A, Tylki-Szymanska A, Vellodi A, Belmatoug N, Grabowski GA, Kolodny EH et al. Long-term hematological, visceral, and growth outcomes in children with Gaucher disease type 3 treated with imiglucerase in the International Collaborative Gaucher Group Gaucher Registry. Mol Genet Metab. 2017;120:47-56. doi:10.1016/j.ymgme.2016.12.001.
113. Charrow J, Esplin JA, Gribble TJ, Kaplan P, Kolodny EH, Pastores GM et al. Gaucher disease: recommendations on diagnosis, evaluation, and monitoring. Arch Intern Med. 1998;158:1754-60.
114. Bi Y, Might M, Vankayalapati H, Kuberan B. Repurposing of proton pump inhibitors as first identified small molecule inhibitors of endo-beta-N-acetylglucosaminidase (ENGase) for the treatment of NGLY1 deficiency, a rare genetic disease. Bioorg Med Chem Lett. 2017;27:2962-6. doi:10.1016/j.bmcl.2017.05.010.

Tables.

Table 1 Common characteristics of rare diseases

• Most rare diseases are chronic, severe, and highly disabling conditions that often require life-long treatment.
• Rare diseases severely impair the quality of life of affected people and their families; the emotional and financial burden for affected families is considerable.
• Disease onset is often during childhood. Children, including newborns, infants and toddlers, make up a large proportion of the rare disease population.
• Delayed diagnosis resulting in unnecessary medical interventions and inadequate treatment is a common issue in rare diseases.
• Timely access to treatment is crucial for reducing morbidity and mortality. Failure to recognize and adequately treat many rare diseases can have fatal consequences or result in severe and permanent damage.
• Treatment of rare diseases is challenging and for most rare diseases therapeutic options are still lacking or very limited.
• Poor disease knowledge, lack of expertise among clinicians, and restricted access to available therapies further complicate the management of patients with rare diseases.

Table 2. Main pharmacokinetic characteristics of special patient population [neonate (N, 0-1 month), infant (I, 1 month – 2 years), child (C, 2 – 12 years), elderly (E, >65 years)] with respect to adulthood (age, 18-65 years). Notably, in older people a reduction of funtional reserve (i.e., omeostenosis) of some organs (i.e, liver and kidney) may be also present [108]. Children approaching adolescence are more similar to adults than other special population of patients [109]. Increased (↑), decreased (↓) or variable effects (↑↓) are shown with respect to adult population. Possible influence by rare/orphan disease on main pharmacokinetic processes is presented (see the text for more details).

Special populations				Changes with respect to adults (18 – 65 yr)	Pharmacokinetic process	Orphan/rare diseases
N	I	C	E			
✓	✓		✓	Gastric pH (↑)		
✓	✓		✓	Gastric emptying (↓)		
✓	✓		✓	Intestinal transit and permeability (↑↓)	Absorption	Intestinal transit (↑↓) [110]
✓	✓			Biliary secretion (↓)		
✓	✓	✓		Tissue and body water content (↑)		
✓	✓		✓	Adipose tissue (↑)	Distribution	
✓	✓		✓	Plasma protein (albumin, a1-acid glycoprotein) (↓)		
✓	✓	✓	✓	Phase I and II liver enzymes (↑↓)	Metabolism	Liver metabolism and function (↑↓)[110-114]
✓	✓		✓	Glomerular filtration (↓)	Excretion	
✓	✓	✓	✓	Kidney function (general) (↓)		Comorbidities

Figures

Figure 1. The relationship between the various factors in rare diseases, its management and generic drugs.