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

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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
‘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 neuropathy (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 ($C_{\text{max}}$). 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 $C_{\text{max}}$ 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
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
orphans: 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 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 nonessential 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 \textit{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.
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Compliance with ethical standards

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Tables.

Table 1 Common characteristics of rare diseases

<table>
<thead>
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<th>Characteristics</th>
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<tr>
<td>Most rare diseases are chronic, severe, and highly disabling conditions that often require life-long treatment.</td>
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<tr>
<td>Rare diseases severely impair the quality of life of affected people and their families; the emotional and financial burden for affected families is considerable.</td>
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<tr>
<td>Disease onset is often during childhood. Children, including newborns, infants and toddlers, make up a large proportion of the rare disease population.</td>
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<td>Delayed diagnosis resulting in unnecessary medical interventions and inadequate treatment is a common issue in rare diseases.</td>
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<tr>
<td>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.</td>
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<tr>
<td>Treatment of rare diseases is challenging and for most rare diseases therapeutic options are still lacking or very limited.</td>
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<tr>
<td>Poor disease knowledge, lack of expertise among clinicians, and restricted access to available therapies further complicate the management of patients with rare diseases.</td>
</tr>
</tbody>
</table>
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 functional 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).

<table>
<thead>
<tr>
<th>Special populations</th>
<th>Changes with respect to adults (18 – 65 yr)</th>
<th>Pharmacokinetic process</th>
<th>Orphan/rare diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Gastrointestinal pH (↑)</td>
<td>Absorption</td>
<td>Intestinal transit (↑↓) [110]</td>
</tr>
<tr>
<td>I</td>
<td>Gastrointestinal emptying (↓)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Intestinal transit and permeability (↑↓)</td>
<td></td>
<td></td>
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<tr>
<td>E</td>
<td>Biliary secretion (↓)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Tissue and body water content (↑)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Adipose tissue (↑)</td>
<td>Distribution</td>
<td></td>
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<tr>
<td></td>
<td>Plasma protein (albumin, a1-acid glycoprotein) (↓)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase I and II liver enzymes (↑↓)</td>
<td>Metabolism</td>
<td>Liver metabolism and function (↑↓) [110,114]</td>
</tr>
<tr>
<td></td>
<td>Glomerular filtration (↓)</td>
<td>Excretion</td>
<td>Comorbidities</td>
</tr>
<tr>
<td></td>
<td>Kidney function (general) (↓)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. The relationship between the various factors in rare diseases, its management and generic drugs.

**Orphan/rare diseases**
- FDA, EMA initiatives

**Orphan drugs**
- Patent expiration

**Generic drugs**

- **General issues**
  - Bioavailability of narrow therapeutic index drugs?
  - Same quality as non-generic drug?
  - Decrease in overall costs?

- **‘Specific’ issues**
  - Does it improve patients’ outcome?
  - Lack of clinical data
  - Children are under-represented
  - Negative perception from patients about drug switching