

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

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1 **Abstract**

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

21

22 **Key points**

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

1 **1. Introduction**

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

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

21 The introduction of economic and regulatory incentives by governments and health
22 authorities worldwide to encourage the development of treatments for rare diseases has
23 resulted in the approval of an increasing number of so-called ‘orphan drugs’ [9, 11]. Orphan
24 drugs are usually very expensive and the costs of rare disease treatments have raised concern
25 [12, 9]. As the period of patent protection and marketing exclusivity is currently expiring for

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

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

17

18 **2. Methods**

19 A comprehensive search of the peer-reviewed literature was performed in PubMed using
20 combinations of the terms ‘rare disease’, ‘ultra-rare disease’, ‘orphan disease’, ‘orphan drug’,
21 ‘generic drug’, ‘generic substitution’ and ‘bioequivalence’. Terms like ‘children’, ‘pediatric
22 patients’, ‘vulnerable patients’, and ‘fragile patients’ were also included in the search because
23 of the high prevalence of children in the population affected by rare diseases and treated with,
24 or eligible to orphan drugs. Terms related to ‘biosimilars’ were [also](#) included in the search,

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

8

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

10 The definition of rare disease varies across countries. In the USA, a disease is defined as rare
11 when it affects less than 200,000 people in the country; in the EU, a rare disease is a life-
12 threatening or chronically debilitating condition affecting less than 5 in 10,000 people [18].
13 There is currently no official definition of ultra-rare diseases. In the UK, the term describes
14 conditions with a prevalence less than 1 in 50,000 people [19]. A prevalence of <10 in
15 1 million people has also been suggested for defining ultra-rare diseases [20, 21]. In ultra-rare
16 diseases, drug research and development, as well as patient management, are even more
17 difficult than in rare diseases [20-24]. Overall, the exact prevalence and the burden of rare
18 diseases are unknown as epidemiology studies are lacking. Some rare diseases, for example
19 mucopolysaccharidoses (a group of inherited metabolic diseases), have been more
20 extensively investigated than others and attempts to improve epidemiologic data collection
21 are beginning to emerge [25, 26].

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

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

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

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

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

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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

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

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

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

20

21 **5. Current regulations for the approval of generic drugs**

22 Generic drugs are an important component of measures undertaken to reduce healthcare costs
23 [17]. The main reason why the generics of small-molecule drugs usually cost less than their
24 branded counterpart is because in order to obtain marketing authorization it is sufficient to

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

5 *5.1 Bioequivalence studies*

6 Bioequivalence testing is the cornerstone of USA and EU regulatory pathways leading to the
7 approval of small-molecule generics. Bioequivalence is defined as the absence of a
8 significant difference in the rate and extent to which the active ingredient in pharmaceutical
9 equivalents or pharmaceutical alternatives becomes available at the site of drug action when
10 administered at the same molar dose under similar conditions (whereby a pharmaceutical
11 alternative is a product containing the same active compound but differing in chemical form
12 [salt, ester, etc.] of that compound or in the dosage form or strength) [53, 52]. This means
13 that the bioavailability of the two products must be similar. The parameters used to measure
14 bioavailability include the area under the plasma concentration-time curve (AUC) and the
15 maximal plasma concentration (C_{\max}). Studies evaluating these two parameters are performed
16 in healthy volunteers. Average bioequivalence is established if the 90% confidence interval
17 (CI) for the geometric mean of both the AUC and C_{\max} for the generic product are within
18 80% and 125% of the corresponding parameters for the innovator product [52, 53].

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

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

11

12 *5.2 Limitations of current procedures of generic approval*

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

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

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

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

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

10 *5.3 Problematic generic substitutions*

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

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

1 weeks in patients receiving the two levothyroxine formulations [67]. Lack of efficacy in
2 controlling TSH levels with levothyroxine generics has been reported also by the Medicines
3 and Healthcare Products Regulatory Agency in the UK [2]. As a consequence of these
4 reports, levothyroxine generic substitution is not recommended in children with severe
5 congenital hypothyroidism, particularly in those aged <3 years because of the crucial role of
6 TSH on brain development in this age-group [67]. Interestingly, hypothyroidism, which is not
7 a therapeutically complex condition, can be characterized by gastrointestinal dysmotility [31]
8 responsible for the alteration of levothyroxine absorption. Therefore, the accepted variability
9 of a generic product in healthy volunteers could not be comparable to that observed in
10 patients affected by an orphan disease with multisystemic involvement.

11 Other examples of multisystemic orphan disease and NTI drugs are available.

12 Lymphangiomyomatosis affects several organs including liver parenchyma and kidneys
13 [70]. Sirolimus, an orally administered NTI drug, is an FDA-approved treatment of this rare
14 disease, but it displays a “wide inter- and inpatient variability in drug clearance” [71],
15 hence changes in liver and kidney functions can alter its pharmacokinetics. Similar concerns
16 have been raised by several researchers regarding the use of generic tacrolimus in
17 transplanted patients [72, 73], and well-designed bioequivalence studies that include
18 transplant patients are needed [74].

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

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

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

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

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

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

6 Despite the evaluation process held by the EMA and FDA, concerns related to the
7 administration of biosimilars are even greater than for chemical generics, because of the
8 quality of the biosimilars and their immunogenicity. Indeed, the incidence of antidrug
9 antibodies depends on both biosimilar characteristics (i.e., production and purification
10 processes, storage and handling) and factors associated with the patient and his/her disease
11 (i.e., route of administration, frequency and duration of treatment) [83-85]. Glycosylation is
12 essential for the biological activity of erythropoietins (EPOs) [86], but the the pattern of
13 glycosylation (number of residues and complexity of carbohydrate structures) depends on the
14 cellular system used for the synthesis [87]. Indeed, EPO biosimilars can differ in
15 glycosylation with respect their originators, and this was thought to be clinically irrelevant
16 [88]; however, two EPO biosimilars presented a dissimilar glycosylation profile with respect
17 to the originator and a different immunogenicity profile when tested in preclinical models
18 [85]. Some authors believe that using an international nonproprietary name (INN) for these
19 biosimilars will facilitate their use and postmarketing control [89]. Interestingly, recombinant
20 human granulocyte colony-stimulating factor (rhG-CSF) can be used in its glycosylated
21 (lenograstim) and non-glycosylated form (filgrastim) because glycosylation seems to be non
22 essential for its biological activity, rather for proteolytic stability and prevention of aggregate
23 formation [90]. For that reason, recent efforts have been focussed on the production of a fully
24 synthetic aglycone G-CSF with predefined carbohydrate structures [91].

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

18 Overall, the main issue for biosimilars is their therapeutic equivalence and interchangeability
19 with respect to originators, because the process of bioequivalence is complex. In order to
20 overcome this issue, FDA guidelines report the correct way in which interchangeability of
21 biosimilars, with respect to originators, should be demonstrated in clinical trials
22 [UCM537135]. Other authors are suggesting that real world data, pharmacovigilance
23 protocols and prospective studies will also help in the growth of knowledge on biosimilars
24 [55]. However, pharmacovigilance databases may be inadequate in rare diseases, thus fueling
25 the search for new tools of analysis [94].

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

10

11 **6. Discussion and conclusions**

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

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

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

5 Although the high costs of orphan drugs remain an unresolved and intensely debated
6 problem, cost is not the only cause of limited access to treatment. Other less recognized
7 causes include the inadequacy and redundancy of pricing and reimbursement policies
8 worldwide that clearly result in delayed and partial access to treatment [49, 50, 97].

9 According to general consensus among orphan drug experts, such policies urgently need
10 revision, to improve their flexibility and the rapidity of decision-making. The difficulties of
11 decision-making about orphan drugs largely come from the uncertainties surrounding the
12 clinical benefits of the treatment. In this respect, it has been suggested that patients should be
13 considered important sources of information that could contribute to reducing the
14 uncertainties about orphan drugs [97].

15 Some information suggests that the focus on the high acquisition costs of orphan drugs may
16 be excessive. An opinion paper recently published by EURORDIS has highlighted that the
17 attention given to the costs of orphan drugs often overshadows other relevant and unresolved
18 issues, which have a less prominent position in the public debate about the treatment of rare
19 diseases [98]. Such issues include patient- and disease-centered problems like the
20 improvement of patient outcome, the lack of clinical data, the under-representation of
21 children, as well as insufficient disease knowledge for most rare and ultra-rare conditions.

22 Regarding the real costs of rare disease treatments, evidence from studies conducted in
23 Europe and elsewhere suggests that the impact of orphan drug costs on national healthcare
24 budgets is relatively limited and usually below 6% of national budgets for medicines [99-
25 103]. As noted in a recent paper that has investigated the problems associated with the access

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

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

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

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

3

4

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8

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1 **Tables.**

2 **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.

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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., homeostasis) 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, α1-acid glycoprotein) (↓)		
✓	✓	✓	✓	Phase I and II liver enzymes (↑↓)	Metabolism	Liver metabolism and function (↑↓) [110-114]
✓	✓		✓	Glomerular filtration (↓)	Excretion	
✓	✓	✓	✓	Kidney function (general) (↓)		Comorbidities

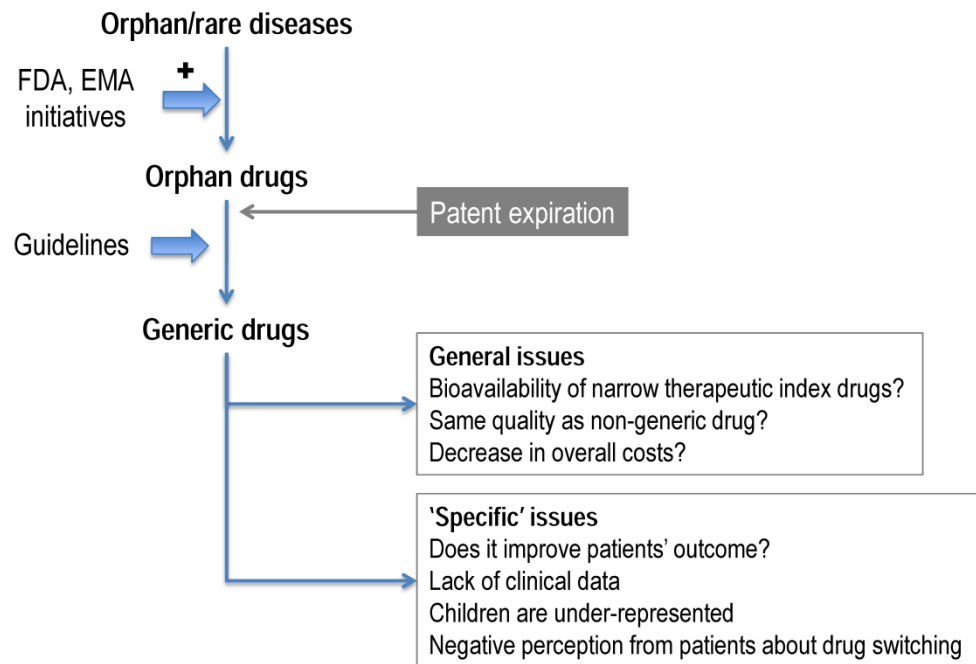
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1 **Figures**

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

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