European Journal of Neurology

european journal of neurology
the official journal of the european academy of neurology

REVIEW ARTICLE OPEN ACCESS

Generics, Biosimilars and Follow-On Non-Biologic Complex Drugs for Multiple Sclerosis: A Narrative Review of the Regulatory and Clinical Implications for European Neurologists

Thomas Berger[1] | Markus Zeitlinger[2] | Veronica Popescu[3,4] | Melinda Magyari[5,6,7,8] | Laura Airas[9] | Mona Alkhawajah[10] | Maura Pugliatti[11] | Magd Zakaria[12] | Carlo Pozzilli[13] | Jelena Drulovic[14] | Bart Van Wijmeersch[3,4] | Patrick Vermersch[15] | Celia Oreja-Guevara[16,17]

[1]Department of Neurology and Comprehensive Center for Clinical Neurosciences and Mental Health, Medical University of Vienna, Vienna, Austria | [2]Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria | [3]University MS Center, Hasselt-Pelt, Noorderhart Hospital, Belgium | [4]Hasselt University, Hasselt, Belgium | [5]Danish Multiple Sclerosis Center, Glostrup, Denmark | [6]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark | [7]The Danish Multiple Sclerosis Registry, Department of Neurology, Copenhagen University Hospital—Rigshospitalet, Glostrup, Denmark | [8]Institute for Clinical Medicine, University of Copenhagen, Copenhagen, Denmark | [9]University of Turku, Turku, Finland | [10]Neuroimmunology Integrated Practice Unit, Neuroscience Center, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia | [11]University of Ferrara, Ferrara, Italy | [12]Ain-Shams University, Cairo, Egypt | [13]University of Roma La Sapienza, Rome, Italy | [14]University of Belgrade, Belgrade, Serbia | [15]University of Lille, Inserm U1172, Lille Neuroscience & Cognition Research Centre (LilNCog), CHU Lille, FHU Precise, Lille, France | [16]Department of Neurology, Hospital Clínico San Carlos, IdISSC, Madrid, Spain | [17]Department of Medicine, Complutense University of Madrid, Madrid, Spain

Correspondence: Celia Oreja-Guevara (orejacbn@gmail.com)

Received: 12 September 2024 | **Revised:** 28 November 2024 | **Accepted:** 20 March 2025

Funding: This work was supported by ParadigMS.

Keywords: biosimilars | generics | multiple sclerosis | non-biologic complex drugs | regulatory approval

ABSTRACT

Background: Multiple sclerosis (MS) places substantial socioeconomic burden on patients due to its early onset and progressive nature, but healthcare systems are also impacted by the high costs of disease-modifying treatments (DMTs). The use of generics (for conventional drugs), biosimilars (for biologics) or follow-on versions of non-biologic complex drugs (NBCDs) can help to reduce the cost of MS care and improve patient access. This review describes the European regulatory processes for these DMT 'copies' and the available data in people with MS.

Methods: A PubMed literature search was undertaken in March 2024, using the terms 'biosimilar', 'generic', 'non-biologic complex drug', 'NBCD' and 'follow-on' in association with 'multiple sclerosis'.

Results: Our literature search identified three clinical studies with generic treatments for MS (two with generic fingolimod and one with generic dimethyl fumarate), 11 studies with biosimilars (eight with biosimilar interferon formulations, one with natalizumab and two with rituximab biosimilars) and six studies with follow-on glatiramer acetate. The data showed that the generics, biosimilars and follow-on NBCDs had similar clinical efficacy and tolerability profiles to the originator drugs, although the quality and quantity of the research varied between DMTs.

Thomas Berger and Celia Oreja-Guevara have contributed equally to this work.

Conclusions: In Europe, there are robust regulatory processes for generics, biosimilars and follow-on NBCDs, in order to ensure that these agents can be considered equally effective and safe as the originator DMT. Physicians caring for people with MS should familiarise themselves with the evidence so that they can have informed conversations about the potential use of these agents.

1 | Introduction

Multiple sclerosis (MS) is a chronic progressive disease with onset usually in early to mid-adulthood. The global average age at MS onset is 32 years [1], although this appears to be increasing over time [2–4]. Because of the early age at onset and the progressive clinical course, the lifetime burden of MS is considerable for the affected individual, their families and society [1]. Both direct and indirect medical costs are high because the working lives of patients are often affected by symptoms, relapses and/or disability [5], and these costs increase over time as patients accrue disability [6].

Disease-modifying treatments (DMTs) have significantly improved the lives of people with MS (PwMS) by reducing the frequency of relapses and slowing disability progression [7]. However, DMTs are a major contributor to the economic burden of MS, with recent estimates that drug costs account for 60%–90% of the direct healthcare costs associated with treating MS [6, 8]. Other direct healthcare costs of MS include those associated with hospitalizations, outpatient services, diagnostics and medical procedures, while indirect healthcare costs include the productivity losses associated with increasing absenteeism and progressive disability in PwMS.

Many of the original DMTs used for MS have come off patent, allowing the development of generics (for conventional small-molecule drugs), biosimilars (for biologics) or follow-on versions of non-biologic complex drugs (NBCDs). The cost of developing these agents is lower than the cost of developing the originator product, and the use of generics, biosimilars or follow-on NBCDs can substantially reduce the overall cost of MS care for payers [5, 9, 10].

The regulatory process for DMT 'copies' differs depending on whether the agent is a generic (such as teriflunomide, dimethyl fumarate [DMF] or fingolimod), a biosimilar (such as interferon [IFN] formulations or natalizumab) or a follow-on NBCD (such as glatiramer acetate [GA]). The aim of this article is to explain and clarify the terminology and European regulatory processes for these DMT copies, and describe the clinical data for these agents, so that neurologists and PwMS can make informed treatment decisions.

2 | Methods

A search of the PubMed database was undertaken on 4 March 2024, using the terms: 'biosimilar', 'generic', 'non-biologic complex drug', 'NBCD' and 'follow-on' in association with 'multiple sclerosis'. No date limits were set. The titles and abstracts were reviewed for relevance. Only articles examining the use of drugs for relapsing–remitting MS (RRMS) currently available in the European Union (EU) were included. Articles describing studies that were conducted in countries outside Europe were considered for inclusion because the results of such studies are relevant to this review. However, it is acknowledged that the characteristics of the healthcare systems, patient populations and drug manufacturing standards in non-European countries may differ from those in European countries. Review articles were evaluated for inclusion, but the 'Clinical considerations' section of this article included only clinical studies.

3 | Definitions

The European Medicines Agency (EMA) definition for a generic drug is "*... a medication that is developed to be the same as a medicine that has already been authorised. Its authorisation is based on efficacy and safety data from studies on the authorised medicine*" [11]. The United States (US) Food and Drug Administration (FDA) definition is a little more detailed, stating that a generic is "*... a drug created to be the same as an already marketed brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use*" [12].

Biologic drugs are produced by biological organisms. They are more complex molecules than synthetic drugs and there is an inherent degree of minor variability (microheterogeneity) between molecules. Therefore, it is not possible to manufacture a biologic that is identical to the originator (unlike a synthesised generic molecule) [13]. Hence, the term 'biosimilar' is used to refer to a follow-on version of a biologic treatment. The EMA defines a biosimilar as "*... a biological medicine highly similar to another biological medicine already approved in the EU (called 'reference medicine') in terms of structure, biological activity and efficacy, safety and immunogenicity profile (the intrinsic ability of proteins and other biological medicines to cause an immune response)*" [13].

NBCDs are neither small-molecule synthetic drugs nor biologic agents [14]. Instead, they comprise high-molecular weight molecules and nanoparticular elements, such as liposomes or copolymer micelles. Because the whole complex is the active pharmaceutical ingredient, it is impossible to fully characterise the molecular and pharmacological properties of an NBCD using only physicochemical analysis [15]. The 'generic' versions of NBCDs are often called 'follow-on' products, since they do not meet the criteria for generics or biosimilars; the term 'follow-on NBCD' is used throughout this article. There is no official definition for a follow-on NBCD, but manufacturers must have a robust process to reliably reproduce a product with the same biofate (i.e., the same biological activity and pharmacokinetic properties) as the originator product [15].

Table 1 shows the DMTs typically used in the treatment of MS in Europe, including those that have generic, biosimilar and follow-on versions, identified by a search of the EMA website (https://www.ema.europa.eu/en/homepage). Information on DMTs available for use in the US, as identified from a search of the FDA website (https://www.fda.gov/), is included for comparison.

TABLE 1 | Disease-modifying treatments for multiple sclerosis, including follow-on versions, approved by the EMA and US FDA.

	EMA		US FDA	
Disease-modifying treatment	**Originator brand (company)**	**Follow-on version (trade names [indicated by] or company)**	**Originator brand (company)**	**Follow-on version (trade names [indicated by] or company)**
Synthetic molecules				
Teriflunomide	Aubagio (Sanofi)	Accord and Mylan	Aubagio (Sanofi)	Natco, Alembic, Hetero, Apotex, MSN, Aurobindo, Biocon, Glenmark, Zydus, Sola, Accord, Torrent, Teva and Sandoz
Dimethyl fumarate	Tecfidera (Biogen)	Accord, Mylan and Neuraxpharm	Tecfidera (Biogen)	Anda, Cipla, Glenmark, Macleods, TWI Pharms, Aurobindo, Amneal, Princeton, Sola, Alkem, MSN, Accord, Hetero and Mylan
Diroximel fumarate	Vumerity (Biogen)	—	Vumerity (Alkermes)	—
Cladribine	Mavenclad (Merck)	—	Mavenclad (Serono)	Hikma, Fresenius and Hisun
Fingolimod	Gilenya (Novartis)	Accord and Mylan	Gilenya (Novartis)	Hetero, HEC, EZRA Ventures, Biocon, Aurobindo, Glenmark, Accord, Apotex, Zydus, Dr. Reddy's, Prinston, Alkem, Mylan, Teva, Sun and Bionpharma
Siponimod	Mayzent (Novartis)	—	Mayzent (Novartis)	—
Ozanimod	Zeposia (BMS)	—	Zeposia (Bristol)	—
Mitoxantrone	Not approved	—	Novantrone (EMD Serono) – no longer used	Fresenius Kabi, Hikma, Hospira and Meitheal
Biologics				
IFN-β1b	Betaferon (Bayer), Extavia (Novartis)	—	Betaseron (Bayer)	—
IFN-β1a	Avonex (Biogen); Rebif (Merck)	—	Avonex (Biogen); Rebif (Serono)	—
PEG-IFN-β1a	Plegridy (Biogen)	—	Plegridy (Biogen)	—
Natalizumab	Tysabri (Biogen)	Tyruko	Tysabri (Biogen)	Tyruko
Alemtuzumab	Lemtrada (Sanofi)	—	Lemtrada (Genzyme)	—

(Continues)

TABLE 1 | (Continued)

Disease-modifying treatment	EMA		US FDA	
	Originator brand (company)	Follow-on version (trade names [indicated by] or company)	Originator brand (company)	Follow-on version (trade names [indicated by] or company)
Rituximab	MabThera (Roche)	Truxima Ritemvia, Rixathon, Riximyo, Blitzima	Rituxan (Genentech)	Truxima, Ruxience, Riabni
Ublituximab	Briumvi (Neuraxpharm)	—	Briumvi (TG Therapeutics)	—
Ocrelizumab	Ocrevus (Roche)	—	Ocrevus (Genentech)	—
Ofatumumab	Kesimpta (Novartis)	—	Kesimpta (Novartis)	—
Non-biologic complex drugs				
Glatiramer acetate	Not approved	—	Copaxone (Teva)	Mylan and Sandoz

Abbreviations: BMS, Bristol Myers Squibb; EMA, European Medicines Agency; IFN, interferon; PEG, pegylated; US FDA, United States Food and Drug Administration.

4 | Regulatory Requirements

4.1 | Generics

In Europe, generics may be approved centrally by the EMA or via decentralised processes (i.e., national approval in a single EU member state and then expanded to other countries via the mutual recognition procedure, or simultaneous applications in more than one EU member state). The application does not require preclinical and clinical studies for the generic agent, but must include bioequivalence study data [16].

The term 'bioequivalence' means no significant difference in plasma exposure (defined by maximal plasma concentration [C_{max}] and area under the concentration-time curve [AUC]) between the generic and the originator, using appropriate bioavailability studies [16]. In Europe, bioequivalence is judged according to the ratio of the test product's and reference product's C_{max} and AUC. For the two products to be considered bioequivalent, the lower bound of the 90% confidence interval (CI) for the ratio must be $\geq$80.00% and the upper bound $\leq$125.00% [17]. For agents with a narrow therapeutic index, where small dose changes can greatly impact clinical outcomes, the EMA recommends tightening the acceptable lower and upper bounds to $\geq$90.00% and $\leq$111.11%, respectively [17]. Overall, bioequivalence studies must demonstrate minimal difference in the mean exposure of a generic versus its originator in a well-defined population.

The approval of a generic drug in Europe will include all licensed indications as approved for the originator product [16].

4.2 | Biosimilars

As described earlier, the microheterogeneity of biologic medicines makes it impossible to manufacture a biosimilar that is identical to the originator [13]. Because of this key difference between biosimilars and generic medicines, the regulatory requirements for approval are not the same (Table 2) [13]. In Europe, all biosimilars must be approved centrally by the EMA; they cannot be approved in individual member states using decentralised processes.

Manufacturers of biosimilars must demonstrate that minor variability (between the biosimilar and its originator, and also between batches of the biosimilar product) does not affect the efficacy or safety of the biosimilar [13]. The main sources of variability in biologic drugs are post-translational modifications and protein aggregate content.

Common post-translational modifications include glycosylation (i.e., sugar molecules attached to the protein), phosphorylation, oxidation, lipidation, sulphation, the formation of disulphide bonds and deamidation [18]. Small differences in glycosylation patterns are permitted [13], but any differences in terminal amino acid residues must be shown to have no biological relevance to safety or efficacy [19].

The biosimilar and originator biologic must show the same primary amino acid sequence and the same protein folding

TABLE 2 | Comparison of the characteristics and development of generic drugs and biosimilars [13].

Generic medicines	Biosimilars
Usually produced by chemical synthesis	Obtained from a biological source
Generally possible to obtain exactly the same molecule	Possible to produce a molecule to a high degree of similarity due to unique biomanufacturing methods and natural biological variability
Mostly smaller molecules, easier to characterise	In general, larger, structurally more complex molecules, which require multiple technologies for their characterisation
Full data requirements on pharmaceutical quality	Full data requirements on pharmaceutical quality, plus additional quality studies comparing the structure and biological activity of the biosimilar with the reference medicine
Development based on demonstration of bioequivalence (i.e., that the generic and the reference medicine release the active substance into the body at the same rate and to the same extent under similar conditions)	Development based on demonstration of biosimilarity using comparability studies (comprehensive head-to-head comparison of the biosimilar with the reference medicine to show high similarity in chemical structure, biological function, efficacy, safety and immunogenicity)
Clinical data requirements are mainly pharmacokinetic bioequivalence studies	In addition to comparative pharmacokinetic and pharmacodynamic studies, safety and efficacy may be required, particularly for more complex biological molecules
All indications approved for the reference medicine can be granted based on demonstrated bioequivalence, without the need for further clinical data	Efficacy and safety have to be justified in each indication. However, confirmatory clinical trials with the biosimilar are usually not needed in every indication that has been approved for the reference medicine. After demonstration of biosimilarity, extrapolation of data to other indications is possible if the scientific evidence available addresses all specific aspects of these indications

pattern [13], using 3-dimensional structural characterisation [18]. Quality analysis must demonstrate that post-translational modifications are similar in the biosimilar and originator biologic using mass spectrometry and peptide mapping, and specifically that protein folding has not been affected by post-translational modifications [18, 19].

Protein aggregates are a concern in biologic products because they may affect immunogenicity and toxicity [18]. Therefore, the biosimilar must be tested for the presence of aggregates, commonly using size exclusion chromatography or spectrometry [18].

The complexity of the molecules and formulations means that the regulatory process for biosimilars usually requires the following information [13, 18]: (1) the pharmaceutical quality of the biosimilar; (2) biosimilarity with the originator biologic in comparative non-clinical studies (chemical structure, biological function/activity); (3) clinical comparability (pharmacokinetics, pharmacodynamics, efficacy, safety, immunogenicity); and (4) a risk management plan. Deviations from this approach are possible but need to be discussed with the EMA upfront. Some differences in posology and route of administration between the biosimilar and the originator biologic may be allowed if this has no effect on the efficacy and safety of the biosimilar [13].

Compared with the regulatory process for an originator biologic, the regulatory process for a biosimilar requires more preclinical research to demonstrate comparability and less clinical research (Figure 1) [20]. Efficacy and safety of the biosimilar must be justified for each indication but not necessarily demonstrated (i.e., efficacy and safety in one indication is commonly extrapolated to others after demonstrating biosimilarity) [13].

The risk management plan is important for ensuring long-term consistency of product manufacturing. With any biologic medicine (originator or biosimilar), there is a risk of "drift" in biological properties. A major example of drift was identified with trastuzumab for breast cancer, whereby drift led to changes in the properties of the biologic which negatively affected its cytotoxicity and efficacy [21]. Therefore, ongoing monitoring of batch consistency and product safety is important for both originator and biosimilar biologics.

4.3 | Follow-On NBCDs

Follow-on NBCDs are neither biologics nor small-molecule pharmaceuticals, and there is no specific regulatory process for their approval [22]. In Europe, follow-on NBCDs may be approved via decentralised processes [22], similar to generics. However, regulatory approval tends to follow the procedure for biosimilars more closely, in which sensitive methods are required to comprehensively characterise physicochemical characteristics and demonstrate the equivalent quality of the complex molecules in the originator and the follow-on NBCD [23]. In 2021, the FDA and EMA launched a pilot program to align the regulatory evaluations for follow-on NBCDs in the US and Europe, in order to optimise the application process [24].

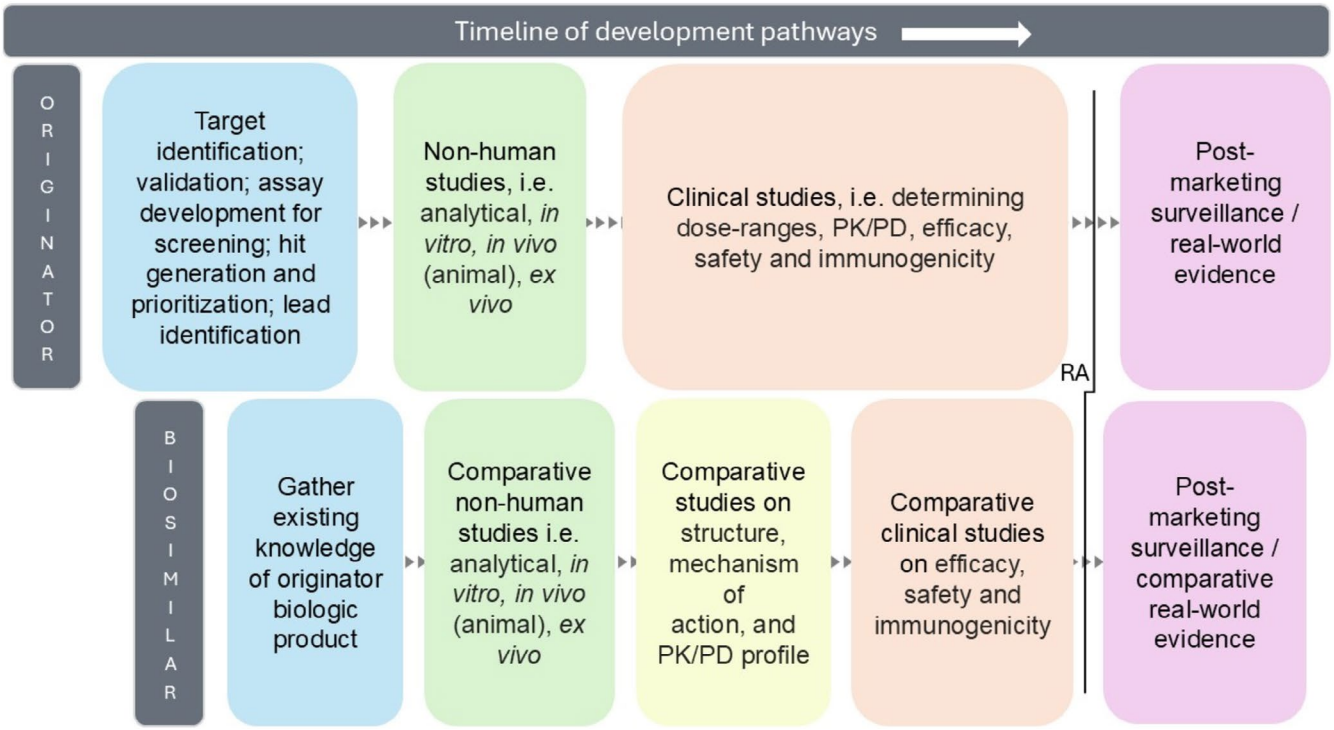

FIGURE 1 | Typical regulatory and development pathway for the originator biologic and its biosimilar [20]. *Non-human studies including analytical, in vitro, in vivo (animal) and ex vivo studies. PD, pharmacodynamic; PK, pharmacokinetic.

Differences in the regulatory processes for generics, biologics and follow-on NBCDs affect their availability. The availability of biosimilars, which must be approved centrally, is consistent throughout the EU, but the availability of generics and follow-on NBCDs may differ between European countries.

5 | Clinical Considerations

5.1 | Generics

Our literature search identified three clinical studies of generic treatments for MS: two with generic fingolimod and one with generic DMF [25–27]. In all three studies, PwMS were switched to the generic DMT from another form of DMT; in other words, none were switched from the originator to the generic [25–27].

The two studies with fingolimod were conducted in Turkey and were retrospective analyses of PwMS who received generic fingolimod in real-world clinical practice for at least 1 year ($n = 263$) [26] or at least 2 years ($n = 508$) [27]. In both studies, generic fingolimod demonstrated similar efficacy and safety to the reported efficacy and safety of originator fingolimod in clinical trials. However, neither study included a comparator or control group, so no direct comparisons with the originator molecule could be made [26, 27].

The analysis of generic DMF was undertaken in Iran and was another real-world retrospective analysis without a control group [25]. Generic DMF was effective in controlling relapses and maintaining Expanded Disability Status Scale (EDSS) scores. Overall, 15/142 patients (10.5%) discontinued treatment within a year, mostly because of adverse events (AEs; 8/15; 53.3%), but also because of relapse (5/15; 33.3%) or pregnancy (2/15; 13.3%) [25]. The authors note that the observed discontinuation rate was lower than has been reported in many other DMF studies, possibly because they slowly titrated the dose to minimize early gastrointestinal (GI) AEs [25].

In 2023, a report was received of a 50-year-old patient on teriflunomide who was switched from the originator (Aubagio) to a generic product [28]. Two months later she had experienced abdominal numbness and tingling, and leg muscle weakness. Independent laboratory testing revealed that, in comparison to two other generic products (that contained 99.1%–101.2% teriflunomide) or Aubagio (100.8% teriflunomide), the generic product that the patient had been taking contained 55.5% teriflunomide. This is well below the FDA specifications for the content of teriflunomide tablets [28].

5.2 | Biosimilars

We identified eight clinical studies with biosimilar IFN formulations [29–36], one with natalizumab [37] and two with rituximab [38, 39]. Seven of these studies (four with IFN-β1a and one each with IFN-β1b, natalizumab and rituximab) prospectively compared the biosimilar with the originator biologic and are summarised in Table 3.

5.2.1 | Interferon-β1a

Two comparative studies used intramuscular (IM) IFN-β1a (Avonex) and its biosimilar (CinnoVex) and reported the data in three publications [29, 34, 36]. There were no statistically significant differences between the originator IFN-β1a and the

TABLE 3 | Studies that prospectively compared biosimilars and follow-on glatiramer acetate with the originator products.

Reference	Design	Treatments	*N*	Duration (months)	Major endpoints	Key results
IFN-β1a						
Abolfazli et al. 2012 [29]	Non-R, prospective, OL	Avonex vs. CinnoVex	34 vs. 43	12	QoL, EDSS	No statistically significant differences in EDSS or MSQoL54 scores
Nafissi et al. 2012 [34]	R, DB	Avonex vs. CinnoVex	42 vs. 42	24	EDSS, relapses, MRI parameters, AEs	No statistically significant differences in EDSS, relapse rate, MRI parameters at 24 months; incidence and duration of arthralgia, oral ulcers, headache and AST/ALT increases were higher with Avonex vs. CinnoVex ($p < 0.05$)
Shakharami et al. 2013 [36]	R, DB	Avonex vs. CinnoVex	42 vs. 42	24	NAb levels	No difference in NAb positivity rates
Boyko et al. 2019 [31]	R, blinded, PC then OL	Rebif vs. Teberif vs. placebo, then all on Teberif	56 vs. 53 vs. 56, then 138	24	MRI parameters	Both forms of IFN-β1a were significantly better than placebo at week 16; no significant difference in MRI parameters or safety/tolerability between Rebif and Teberif at any timepoint
IFN-β1b						
Khabirov et al. 2012 [32]	OL, observational[a]	Betaferon vs. Ronbetal	285 vs. 316	NR	Relapses, EDSS	No significant differences in clinical parameters between the groups; transient flu-like symptoms were more common in patients receiving Ronbetal vs. Betaferon (89.6% vs. 50.9%; $p < 0.05$)
Natalizumab						
Hemmer et al. 2023 [37]	R, DB	Originator natalizumab vs. PB006	133 vs. 131	10.2[b]	MRI parameters at week 24, EDSS at week 24 and 48, ARR	No significant difference in MRI parameters, ARR, EDSS score or AE incidence
Rituximab						
Perez et al. 2020 [39]	Observational[c]	MabThera vs. Truxima	105 vs. 45	12	CD19+ lymphocyte counts, EDSS	No statistically significant differences in CD19+ lymphocyte counts, ARR, EDSS score or AE incidence
GA						

(Continues)

TABLE 3 | (Continued)

Reference	Design	Treatments	*N*	Duration (months)	Major endpoints	Key results
Cohen et al. 2015 [40]	R, DB, PC	Copaxone vs. generic GA vs. placebo	357 vs. 353 vs. 84	9	MRI parameters during months 7–9, ARR, EDSS	Both GA formulations were significantly better than placebo for primary endpoint ($p < 0.001$); no significant differences in efficacy or safety outcomes for generic vs. originator GA
Boyko et al. 2016 [41]	R, DB, PC	Copaxone vs. BCD-063 vs. placebo	61 vs. 61 vs. 28	11.1[d]	MRI parameters, EDSS, MSFC	Both GA formulations were significantly better than placebo for all efficacy endpoints ($p < 0.05$); no significant differences in efficacy or safety outcomes for generic vs. originator GA

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ARR, annualised relapse rate; AST, aspartate aminotransferase; DB, double-blind; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; IFN, interferon; MRI, magnetic resonance imaging; MSFC, Multiple Sclerosis Functional Composite; MSQoL54, Multiple Sclerosis Quality of Life 54-item Questionnaire; NAb, neutralising antibody; NR, not reported; OL, open-label; PC, placebo-controlled; QoL, quality of life; R, randomised.

[a]Patients initiated on IFN-β1b between February 2008 and February 2010 received originator IFN-β1b (Betaferon) and those initiated on IFN-β1b from March 2010 through March 2012 received the biosimilar (Ronbetal).

[b]44 weeks.

[c]Patients initiated on rituximab between December 2015 and October 2017 received originator rituximab (MabThera) and those initiated on rituximab after October 2017 until June 2018 received the biosimilar (Truxima).

[d]48 weeks.

biosimilar in terms of quality of life (QoL), EDSS scores, magnetic resonance imaging (MRI) parameters or neutralising antibody development over 12–24 months [29, 34, 36]. The biologic and biosimilar showed similar tolerability and safety profiles, but one study reported a higher incidence and duration of some AEs (specifically, arthralgia, oral ulcers, headache and increases in liver enzymes) in patients receiving the originator biologic compared with those receiving the biosimilar ($p < 0.05$) [34].

A non-comparative observational study with an IM IFN-β1a biosimilar (Genfaxon) showed that it was well tolerated over 12 months of treatment, but was better tolerated in patients who were naïve to DMTs than in those who had previously received any DMT [30].

One study compared subcutaneous IFN-β1a (Rebif) with the biosimilar Teberif and showed comparable and stable effects of the two products on MRI parameters and disability status over 2 years of treatment [31].

5.2.2 | Interferon-β1b

In the single prospective comparative study, the IFN-β1b biosimilar Ronbetal had similar efficacy to its originator (Betaferon) in terms of relapse rate and EDSS scores, but a significantly higher proportion of patients receiving Ronbetal versus Betaferon developed transient flu-like symptoms during treatment (89.6% vs. 50.9%; $p < 0.05$) [32]. A key limitation of this study was that patients were enrolled consecutively into the two treatment groups (i.e., all received Betaferon in the first 2 years and then all received Ronbetal over the next 2 years), which could have introduced bias.

In the non-comparative or retrospective studies, the biosimilar Infibeta was reported to have good efficacy and tolerability over 52 weeks in 123 adults with MS [35], and over 15–35 (median 26.7) months of treatment in nine adolescents with paediatric-onset MS (aged 14–17 years) [42]. Russian researchers conducted a retrospective analysis of outcomes in PwMS receiving Infibeta ($n = 95$), originator IFN-β1b ($n = 108$), the IFN-β1a biosimilar Genfaxon-44 ($n = 83$), the IFN-β1a biosimilar CinnoVex ($n = 109$) or the GA follow-on Aksoglatiran FS ($n = 105$) [33]. For most endpoints (including annual relapse rates, EDSS score, the proportion of patients without disease activity on MRI, and the proportion of patients with no evidence of disease activity based on combined relapse, EDSS and MRI parameters [NEDA-3] at 12 and 24 months), Infibeta demonstrated effectiveness that was generally comparable with originator IFN-β1b or Genfaxon-44, and greater than CinnoVex or Aksoglatiran FS. Flu-like syndrome was least common in the groups receiving Infibeta or CinnoVex, and injection reactions were most common in the groups receiving Genfaxon-44 or Aksoglatiran FS [33].

5.2.3 | Monoclonal Antibodies

The natalizumab biosimilar PB006 was compared with originator natalizumab in the well-designed Antelope study. This was a phase 3, randomised, double-blind, comparative trial in 264 patients with RRMS [37]. Treatment was for 44 weeks and

observation for 48 weeks, although patients in the originator natalizumab group were re-randomised at week 24, and 30 patients were switched to PB006. The primary endpoint was the cumulative number of new active lesions on MRI at week 24, defined as new gadolinium-enhancing T1-weighted lesions and new/enlarged T2-weighted lesions. No statistically significant differences were noted between the PB006 group and natalizumab group in the primary endpoint, with a least squares mean number of new active lesions of 0.34 in the PB006 group and 0.45 in the natalizumab group; the difference of 0.17 (95% CI −0.61, 0.94) was within the prespecified margins for equivalence [37]. There were also no significant differences between PB006 and natalizumab in any of the secondary efficacy endpoints (other MRI parameters, EDSS score, relapses), safety or tolerability assessments, or immunogenicity parameters (anti-drug antibodies or neutralising antibodies) [37].

Rituximab is used off-label in MS. Our search identified one comparative study and one observational study with rituximab biosimilars [38, 39]. The comparative study, conducted in France, used a non-randomised design; consecutive patients enrolled between December 2015 and October 2017 received originator rituximab and those enrolled after October 2017 until June 2018 received the biosimilar (Truxima) [39]. There were no statistically significant differences between originator rituximab and the biosimilar in terms of CD19+ lymphocyte counts, clinical or MRI parameters, or the incidence of AEs [39]. An observational study from Iran showed that the rituximab biosimilar Zytux was effective and well tolerated in PwMS, but no comparison was made with originator rituximab [38].

Alemtuzumab, ublituximab, ocrelizumab and ofatumumab are approved monoclonal antibodies for the treatment of MS in Europe [43]. Alemtuzumab was approved by the EMA in 2015 as a treatment for RRMS in both treatment-naïve patients and those who experience breakthrough disease while on DMTs. Efficacy and safety have been demonstrated long-term [44]; however, no biosimilars have been developed. Similarly, there have been no biosimilars of ocrelizumab, ofatumumab or ublituximab since their approvals by the EMA in 2018, 2021 and 2023, respectively (Table 1).

5.3 | Follow-On NBCDs

Six studies with follow-on GA were identified: two were randomised, double-blind, placebo-controlled studies (Table 3) [40, 41] and four were observational studies, including a Russian study comparing follow-on GA with originator IFN-β1b and biosimilars of IFN-β1a and IFN-β1b described earlier [33, 45–47].

Both double-blind, placebo-controlled studies showed that the originator and follow-on GA were significantly more effective than placebo across a range of endpoints, including MRI parameters [40, 41]. Two separate follow-on forms of GA were used in these studies: one manufactured by Synthon [40] and one made by BIOCAD [41]. In both studies, there were no differences between the originator GA and follow-on GA in terms of any of the clinical efficacy endpoints or AE profile [40, 41]. In a separate observational study, the BIOCAD follow-on GA (Timexon) was also shown to slow neurodegeneration in the retina ($n = 19$) [47].

The retrospective observational Russian study described earlier suggested that follow-on GA (Aksoglatiran FS; Nativa) was less effective than originator IFN-β1b and biosimilars of IFN-β1a and IFN-β1b [33]. An observational study from Iran showed that the follow-on GA made by the Zahravi Pharmaceutical Company (Copamer) was generally well tolerated among PwMS and had a tolerability profile similar to the published profile of the originator GA [45]. Adherence with follow-on GA was high, with only 8% of patients discontinuing treatment within 1 year. This is much higher adherence than has been reported in the US, where a database analysis of real-world use indicated that only 61.9% of patients were adherent to follow-on GA (Glatopa); most patients who discontinued follow-on GA in the database analysis did so within 4 months of starting it [46].

6 | Role of Biosimilars, Generics and Follow-On NBCDs in MS

The data described above show that generics, biosimilars and follow-on NBCDs have similar clinical efficacy and tolerability profiles to the originator drugs, although the quality and quantity of the research vary between DMTs. This may reflect differences in the regulatory requirements for generics, biosimilars and follow-on NBCDs since biosimilars typically require clinical studies to demonstrate clinical comparability, whereas generics and follow-on NBCDs may not.

The reduced costs of biosimilars, generics and follow-on NBCDs versus originator products, and consequent competitive lowering of the price of originators, may improve access to DMTs for PwMS. However, depending on the product, the cost savings associated with biosimilars, generics and follow-on NBCDs may be modest [48, 49], because the complexities created by introducing these products in the market can create constraints and competition between products, as well as consumer surpluses [50].

Surveys indicate that most healthcare professionals are willing to prescribe biosimilars, but would prefer to initiate treatment with one rather than switch a patient who is stable on a biologic to a biosimilar [51, 52]. In surveys with physicians, some have expressed concern about a lack of experience or confidence with prescribing biosimilars [52, 53]. Others report being worried about indication extrapolation; for example, the effect of a biosimilar on MRI parameters in MS may not be demonstrated if the biosimilar approval was based on efficacy in another indication [54]. In the EU, indication extrapolation must be justified based on the totality of the evidence and an identical mechanism of action across indications [55]. Another EU requirement is that equivalence and clinical comparability have been demonstrated in the most sensitive indication [55].

Another fear physicians have about biosimilars is that a switch will be made at the pharmacy without consultation (automatic substitution) [51], as can happen with generic drugs. The EMA states that *"... once a biosimilar is approved in the EU it is interchangeable, which means the biosimilar can be used instead of its reference product (or vice versa) or one biosimilar can be replaced with another biosimilar of the same reference product"* [56]. In the EU, each member state is responsible for legislation regarding automatic substitution, so neurologists

are encouraged to familiarise themselves with the national policy. Some of these policies require the authorisation of the responsible physician. An additional concern by the authors of this review is that new biosimilars enter the market after being compared to the originator; however, biosimilars have not been tested against each other.

Some data suggest that patient adherence is lower with generic than with originator medications in MS [57], but the reasons for poor adherence are complex and multifactorial and may be influenced by some of the same socioeconomic variables (e.g., treatment affordability) that influence the selection of a generic medication [58–60].

An international consensus group endorsed by the European MS Platform has developed consensus recommendations for the prescribing of generics, biosimilars and follow-on NBCDs in Europe (Table 4) [54]. The overarching principles of these recommendations are that PwMS and clinicians should jointly decide on drug treatment for MS; treatment decisions should consider the context of the specific healthcare system to increase affordability and overall access to DMTs; and PwMS and clinicians

TABLE 4 | Consensus recommendations on follow-on disease-modifying treatments for multiple sclerosis by a multinational task force and endorsed by the European Multiple Sclerosis Platform [54].

Consensus recommendations	LOE[a]	Grade[b]
Evidence		
FO-DMTs should be supported by rigorous analytical, biofunctional and clinical data, as appropriate, for the therapeutic target(s) of each compound	5	D
The data generated to characterise the FO-DMT should be published in peer-reviewed journals	5	D
Treatment and access		
FO-DMTs represent an effective option of the management of MS, intended to reduce treatment costs and improve access to DMTs for PwMS	5	D
FO-DMTs approved in highly regulated areas are intended to be used in the same way as the reference product	1b	D
Adverse reactions and inadequate treatment response to an FO-DMT are anticipated to occur at the same frequency as with the reference product	1b	B
Switching from the reference product to an FO-DMT is appropriate when the FO-DMT has undergone appropriate testing and regulatory review in a highly regulated area	1b	D
Scientific and clinical evidence is lacking for multiple switching and cross-switching among FO-DMTs containing the same compound	5	D
Purported FO-DMTs only approved outside of highly regulated area might not have undergone rigorous testing and review	5	D
At minimum, any decision to substitute DMTs at the pharmacy level should be actively communicated to PwMS and the prescribing clinician	5	D
Vigilance and acquisition of new data		
Pharmacovigilance data should be sought in the same way for FO-DMTs and the reference product, and reported transparently in a timely manner	5	D
The trade name of any DMT formulation should be recorded in the patient files to allow tracking of adverse reactions or inadequate treatment response	5	D
FO-DMTs should be supported by long-term pharmacovigilance data. This should be supplemented by registries involving the relevant stakeholders (manufacturer, healthcare professionals and patients' associations)	5	D
Companies bringing FO-DMTs to the market should commit to improving patient care by acquiring new scientific data beyond that which is required as a minimum to satisfy regulatory authorities, namely, on long-term outcomes and switching	5	D

Note: Brownlee WJ, Wolf C, Hartung HP, Dingermann T, Anshasi N, Clark RA, Trojano M, Selmaj K, Uitdehaag BM, Tur C, Wuerfel J, Dallmann G, Witte J, Sintzel M, Bobrovnikova O, Cohen JA. *Multiple Sclerosis Journal* (28 [14]) pp. 2177–2189. Copyright 2022 by The Authors. Reprinted by Permission of Sage Publications.
Abbreviations: DMT(s), disease-modifying treatment(s); FO-DMT(s), follow-on disease-modifying treatment(s); LOE, level of evidence; MS, multiple sclerosis; PwMS, people with multiple sclerosis.
[a]Oxford Centre for Evidence-Based Medicine level of evidence: 1b, individual randomised controlled trial; 5, expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.
[b]Grade of recommendation: A, based on consistent level 1 evidence; B, based on consistent level 2 or 3 evidence or extrapolations from level 1 studies; C, level 4 studies or based on extrapolations from level 2 or 3 studies; D, level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

should be offered clear information about the approval process for follow-on DMTs in their area. The consensus group states that registration of a follow-on DMT in a highly regulated area (such as the EU) means that it is as efficacious and safe as the reference product when used in accordance with the label information. However, the consensus group also notes the responsibility of manufacturers to quickly provide pre-approval analytical, biofunctional and clinical data, as well as post-approval pharmacovigilance data for public review, so that physicians have the evidence base on which to make their clinical decisions [54].

These principles highlight the importance of robust regulatory processes and effective oversight for generic, biosimilar and follow-on DMTs for MS. However, concerns have been expressed about the approval of such products in resource-limited settings where regulatory processes and post-marketing pharmacovigilance practices are less robust than they are in Europe and the US [61]. As these agents become more widely available, it is the responsibility of physicians caring for PwMS to familiarise themselves with the regulatory environment and clinical data through ongoing education [62], but it should be noted that this only adds to the heavy administrative and educational tasks of neurologists. While some physicians may be hesitant to switch patients to a generic, biosimilar or follow-on DMT, it is important for them to appreciate that these products have undergone robust assessment for bioequivalence, effectiveness and safety, and that real-world evidence is accumulating to support this. Targeted education of physicians about the approval process for and the bioequivalence, effectiveness and safety of generic, biosimilar and follow-on DMTs (including peer-to-peer and team-based discussions of the evidence from trusted sources, such as the peer-reviewed literature) may increase confidence in prescribing these agents and allow physicians to engage in effective discussions with their patients about switching [63, 64]. Additional effectiveness and safety data from real-world studies and engagement of biosimilar manufacturers with physicians would also be beneficial to inform clinical practice and overcome physician prescribing hesitancy [65].

Author Contributions

Thomas Berger: conceptualization, methodology, visualization, writing – review and editing. **Markus Zeitlinger:** conceptualization, methodology, visualization, writing – review and editing. **Veronica Popescu:** conceptualization, methodology, visualization, writing – review and editing. **Melinda Magyari:** conceptualization, methodology, visualization, writing – review and editing. **Laura Airas:** conceptualization, methodology, visualization, writing – review and editing. **Mona Alkhawajah:** conceptualization, methodology, visualization, writing – review and editing. **Maura Pugliatti:** conceptualization, methodology, visualization, writing – review and editing. **Magd Zakaria:** conceptualization, methodology, visualization, writing – review and editing. **Carlo Pozzilli:** conceptualization, methodology, visualization, writing – review and editing. **Jelena Drulovic:** conceptualization, methodology, visualization, writing – review and editing. **Bart Van Wijmeersch:** conceptualization, methodology, visualization, writing – review and editing. **Patrick Vermersch:** conceptualization, methodology, visualization, writing – review and editing. **Celia Oreja-Guevara:** conceptualization, methodology, visualization, writing – review and editing.

Acknowledgments

We would like to thank Catherine Rees who wrote the outline and first draft of this manuscript on behalf of Springer Healthcare. This medical writing assistance was funded by ParadigMS Foundation. ParadigMS Foundation is an independent and non-profit group of European, Middle Eastern and North African neurologist experts in multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMO-SD) and myelin oligodendrocyte glycoprotein antibody disease (MOGAD). The content of this publication is based upon in-depth discussions on this topic by the group members at Expert Meetings. The current list of group members can be consulted at ParadigMS's website.

Conflicts of Interest

Thomas Berger has received honoraria for lectures, advisory boards and consultations from, and participated in meetings sponsored by, Allergan, Bayer, Biogen, Bionorica, Biologix, BMS, Eisai, Janssen-Cilag, Jazz/GW, Horizon, MedDay, Merck, Neuraxpharma, Novartis, Octapharma, Roche, Sandoz, Sanofi, UCB and Teva; has received institutional financial support in the past 12 months by unrestricted research grants from Biogen, Bayer, BMS, Merck, Novartis, Sanofi Aventis and Teva; and has received institutional financial support for participation in clinical trials for multiple sclerosis sponsored by Alexion, Bayer, Biogen, Merck, Novartis, Octapharma, Roche, Sanofi and Teva. Markus Zeitlinger has received speakers' honorary from Sandoz. Veronica Popescu has received honoraria and travel, and research grants from the Research Foundation—Flanders (FWO), Almirall, Biogen, BMS, Janssen Pharmaceutica, Medtronic, Merck, Novartis, Roche, Sanofi-Genzyme and Teva Pharmaceutical. Melinda Magyari has served on scientific advisory boards and as a consultant for, and has received support for congress participation or speakers' honoraria from, Biogen, Sanofi, Roche, Novartis, Merck and Moderna. The Danish MS Registry received research support from Biogen, Genzyme, Roche, Merck and Novartis. Laura Airas has received institutional research support from the Finnish Academy, US National MS Society, Aatos Erkko Foundation, Sanofi Genzyme and Merck; and compensation for lectures and advising from Novartis, Sanofi Genzyme and Merck. Mona Alkhawajah has received speakers' honorarium, educational travel support and/or consultancy fees from Roche, Merck, Sanofi, Biogen, Novartis, Hikma, SAJA, AstraZeneca and Actelion. Maura Pugliatti has received speakers' fees, travel grants and/or research support from Alexion, Biogen, Bristol Myers Squibb, Janssen, Merck, Roche and Sanofi. Magd Zakaria has received speakers' honorary and fees for advisory boards and educational lectures from Sandoz, Bayer, Biogen, Merck, Novartis, Roche and Sanofi. Carlo Pozzilli has served on scientific advisory boards for Novartis, Merck, Biogen, Bristol Meyers Squibb, Roche, Janssen, Genzyme, Alexion and Almirall; has received funding for travel and speakers' honoraria from Biogen, Merck, Janssen, Alexion, Almirall, Genzyme, Roche, Novartis and Alexion; and has received research support from Almirall, Merck, Biogen, Novartis, Bristol Myers Squibb and Roche. Jelena Drulovic has received speakers' fees, travel grants and/or research support from AstraZeneca, Amicus, Bayer, Biogen, Hemofarm, Janssen, Medis, Merck, Novartis, Pharma Swiss, Roche, Sanofi-Genzyme, Teva and Zentiva. Bart Van Wijmeersch has received speakers' fees, travel grants and/or research support from Alexion, Almirall, Biogen, Bristol Myers Squibb, Imcyse, Janssen, Merck, Novartis, Roche, Sanofi and Teva. Patrick Vermersch has received speakers' fees from AB Science, Ad Scientiam, Biogen, Bristol Myers Squibb, Imcyse, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme and Teva; and has received research support from Merck, Novartis and Sanofi-Genzyme. Celia Oreja-Guevara has received speakers' and consultation fees from Alexion, Biogen Idec, BMS, Horizon, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme, Viatris, Neuraxpharm and Teva.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

References

1. D. Jakimovski, S. Bittner, R. Zivadinov, et al., "Multiple sclerosis," *Lancet* 403 (2024): 183–202.

2. A. Habbestad, J. S. Willumsen, J. H. Aarseth, et al., "Increasing Age of Multiple Sclerosis Onset From 1920 to 2022: A Population-Based Study," *Journal of Neurology* 271 (2024): 1610–1617.

3. L. Prosperini, M. Lucchini, S. Ruggieri, et al., "Shift of Multiple Sclerosis Onset Towards Older Age," *Journal of Neurology, Neurosurgery, and Psychiatry* 93 (2022): 1137–1139.

4. L. Romero-Pinel, L. Bau, E. Matas, et al., "The Age at Onset of Relapsing–Remitting Multiple Sclerosis Has Increased Over the Last Five Decades," *Multiple Sclerosis and Related Disorders* 68 (2022): 104103.

5. G. Kobelt, A. Thompson, J. Berg, et al., "New Insights Into the Burden and Costs of Multiple Sclerosis in Europe," *Multiple Sclerosis* 23 (2017): 1123–1136.

6. C. Murley, P. Tinghog, F. S. Teni, et al., "Excess Costs of Multiple Sclerosis: A Register-Based Study in Sweden," *European Journal of Health Economics* 24 (2023): 1357–1371.

7. N. Koch-Henriksen and M. Magyari, "Apparent Changes in the Epidemiology and Severity of Multiple Sclerosis," *Nature Reviews. Neurology* 17 (2021): 676–688.

8. R. Babela and J. Dugas, "Economic burden of multiple sclerosis in Slovakia—from 2015 to 2020," *BMC Health Services Research* 22, no. 1 (2022): 1467, https://doi.org/10.1186/s12913-022-08883-6.

9. D. M. Hartung, "Economics and Cost-Effectiveness of Multiple Sclerosis Therapies in the USA," *Neurotherapeutics* 14 (2017): 1018–1026.

10. V. M. Rivera, "Biosimilar Drugs for Multiple Sclerosis: An Unmet International Need or a Regulatory Risk?," *Neurology and Therapy* 8 (2019): 177–184.

11. European Medicines Agency, "Generic Medicine,", accessed March 5, 2024, https://www.ema.europa.eu/en/glossary/generic-medicine#:~:text=A%20generic%20medicine%20is%20a,studies%20on%20the%20authorised%20medicine.

12. U.S. Food and Drug Administration, "Generic Drugs: Questions & Answers,", accessed February 22, 2024, https://www.fda.gov/drugs/frequently-asked-questions-popular-topics/generic-drugs-questions-answers.

13. European Medicines Agency, "Biosimilars in the EU: Information Guide for Healthcare Professionals,", accessed February 22, 2024, https://www.ema.europa.eu/system/files/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en_1.pdf.

14. T. Berger, M. Ackerl, E. Auff, et al., "Non-biologic Complex Drugs: Glatiramoide in der Therapie der Multiplen Sklerose," *Neurologische* 3 (2016): 1–6.

15. R. S. Gaspar, B. Silva-Lima, F. Magro, A. Alcobia, F. L. da Costa, and J. Feio, "Non-biological Complex Drugs (NBCDs): Complex Pharmaceuticals in Need of Individual Robust Clinical Assessment Before any Therapeutic Equivalence Decision," *Frontiers in Medicine* 7 (2020): 590527.

16. D. Pierini and K. V. Anderson, "How Generic Drugs Are Made," *US Pharmacist* 38 (2013): 26–31.

17. European Medicines Agency, "Guideline on the Investigation of Bioequivalence,", accessed April 2, 2024, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf.

18. S. Bhojaraj, T. D. A. Kumar, A. R. Ghosh, et al., "Biosimilars: An Overview," *International Journal of Nutrition, Pharmacology, Neurological Diseases* 11 (2021): 7–16.

19. J. Gonçalves, F. Araújo, M. Cutolo, and J. E. Fonseca, "Biosimilar Monoclonal Antibodies: Preclinical and Clinical Development Aspects," *Clinical and Experimental Rheumatology* 34 (2016): 698–705.

20. A. Kulasekararaj, R. Brodsky, A. Kulagin, and J. H. Jang, "Biosimilars in Rare Diseases: A Focus on Paroxysmal Nocturnal Hemoglobinuria," *Haematologica* 108 (2023): 1232–1243.

21. S. Kim, J. Song, S. Park, et al., "Drifts in ADCC-Related Quality Attributes of Herceptin: Impact on Development of a Trastuzumab Biosimilar," *MAbs* 9 (2017): 704–714.

22. K. Klein, P. Stolk, M. L. De Bruin, H. G. M. Leufkens, D. J. A. Crommelin, and J. S. B. De Vlieger, "The EU Regulatory Landscape of Non-biological Complex Drugs (NBCDs) Follow-On Products: Observations and Recommendations," *European Journal of Pharmaceutical Sciences* 133 (2019): 228–235.

23. European Medicines Agency, "Reflection Paper on the Data Requirements for Intravenous Iron-Based Nano-Colloidal Products Developed With Reference to an Innovator Medicinal Product,", accessed February 22, 2024, https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-data-requirements-intravenous-iron-based-nano-colloidal-products-developed-reference-innovator-medicinal-product_en.pdf.

24. European Medicines Agency and Administration USFaD, "Pilot program: EMA-FDA Parallel Scientific Advice for Hybrid/Complex Generic Products—General Principles,", accessed April 2, 2024, https://www.fda.gov/media/152085/download.

25. R. Abolfazli, M. A. Sahraian, A. Tayebi, H. Kafi, and S. Samadzadeh, "Safety and Discontinuation Rate of Dimethyl Fumarate (Zadiva) in Patients With Multiple Sclerosis: An Observational Retrospective Study," *Journal of Clinical Medicine* 12 (2023): 4937.

26. B. Altunan, A. Ünal, H. Efendi, et al., "Use of Follow-On Fingolimod for Multiple Sclerosis: Analysis of Effectiveness and Patient Reported Outcomes in a Real-World Clinical Setting," *Multiple Sclerosis and Related Disorders* 77 (2023): 104880, https://doi.org/10.1016/j.msard.2023.104880.

27. M. Terzi, E. M. Helvaci, S. Şen, et al., "Clinical and Demographic Characteristics and Two-Year Efficacy and Safety Data of 508 Multiple Sclerosis Patients With Fingolimod Treatment," *Noro Psikiyatri Arsivi* 60 (2023): 23–27.

28. D. T. Okuda, K. W. Burgess, T. M. Moog, and M. A. Patel, "Underdosed Generic Specialty Medications: A Prescription for Patient Harm?," *Multiple Sclerosis and Related Disorders* 88 (2024): 105760.

29. R. Abolfazli, A. Hosseini, K. Gholami, M. R. Javadi, H. Torkamandi, and S. Emami, "Quality of Life Assessment in Patients With Multiple Sclerosis Receiving Interferon Beta-1a: A Comparative Longitudinal Study of Avonex and Its Biosimilar CinnoVex," *ISRN Neurology* 2012 (2012): 786526.

30. K. Z. Bakhtiiarova, O. V. Bragina, I. V. Vlasov, et al., "Experience of Using Genfaxon for Treating Patients With Relapsing–Remitting Multiple Sclerosis in The Russian Federation," *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* 114 (2014): 39–45.

31. A. N. Boyko, L. P. Bosenko, V. V. Vasilovskiy, et al., "Efficacy, Tolerability and Safety of the Treatment With Teberif: The Results of a 2-Year Randomized Clinical Trial of Treatment naïve Patients With Remitting Multiple Sclerosis, Who Have Not Received DMT, After Switching From Other Interferon β-1a," *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* 119 (2019): 73–85.

32. F. A. Khabirov, N. N. Babicheva, T. I. Khaibullin, L. A. Aver'ianova, E. V. Granatov, and G. M. Akhmedova, "Biosimilar of interferon-beta 1b in the treatment of multiple sclerosis and the own experience in the use of ronbetal," *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* 112 (2012): 113–122.

33. F. A. Khabirov, T. I. Khaybullin, E. V. Granatov, et al., "The Results of an Open Comparative Retrospective Trial of the Course of Multiple Sclerosis During Treatment With Infibeta and Other Interferon-Beta Bioanalogues and Glatiramer Acetate," *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* 118 (2018): 18–26.

34. S. Nafissi, A. Azimi, A. Amini-Harandi, S. Salami, M. A. shahkarami, and R. Heshmat, "Comparing Efficacy and Side Effects of a Weekly Intramuscular Biogeneric/Biosimilar Interferon Beta-1a With

Avonex in Relapsing Remitting Multiple Sclerosis: A Double Blind Randomized Clinical Trial," *Clinical Neurology and Neurosurgery* 114, no. 7 (2012): 986–989, https://doi.org/10.1016/j.clineuro.2012.02.039.

35. E. V. Popova, A. N. Boĭko, M. V. Davydovskaia, et al., "The First Experience of the Use the Russian Beta-Interferon-1b Biosimilar (Infibeta) in the Daily Practice of the Moscow Center of Multiple Sclerosis," *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* 113 (2013): 93–96.

36. M. A. Shahkarami, B. Vaziri, S. Salami, A. A. Harandi, and J. Oger, "Neutralizing Antibodies in Multiple Sclerosis Patients on Weekly Intramuscular Avonex and Biosimilar Interferon Beta-1a (CinnoVex): Comparing Results of Measurements in Two Different Laboratories," *Journal of Immunological Methods* 388 (2013): 46–48.

37. B. Hemmer, H. Wiendl, K. Roth, et al., "Efficacy and Safety of Proposed Biosimilar Natalizumab (PB006) in Patients With Relapsing–Remitting Multiple Sclerosis: The Antelope Phase 3 Randomized Clinical Trial," *JAMA Neurology* 80 (2023): 298–307.

38. A. Naser Moghadasi, A. Darki, P. Masoumi, S. N. Hashemi, and F. Ghadiri, "Evaluating the Efficacy and Safety of Zytux (Rituximab, AryoGen Pharmed) in Iranian Multiple Sclerosis Patients: An Observational Study," *Multiple Sclerosis and Related Disorders* 36 (2019): 101419.

39. T. Perez, A. Rico, C. Boutière, et al., "Comparison of Rituximab Originator (MabThera) to Biosimilar (Truxima) in Patients With Multiple Sclerosis," *Multiple Sclerosis* 27 (2021): 585–592.

40. J. Cohen, A. Belova, K. Selmaj, et al., "Equivalence of Generic Glatiramer Acetate in Multiple Sclerosis: A Randomized Clinical Trial," *JAMA Neurology* 72 (2015): 1433–1441.

41. A. N. Boyko, N. Y. Lashch, S. N. Sharanova, et al., "Comparative, Placebo-Controlled Clinical Study of Efficacy and Safety of Glatiramer Acetate 20 Mg in Patients With Relapsing–Remitting Multiple Sclerosis: Results of the First Year of the Study," *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* 116 (2016): 61–67.

42. E. V. Popova, A. N. Boyko, O. V. Bykova, I. G. Nankina, and T. T. Batysheva, "Experience of Application of Russian Biosimilar of Interferon Beta-1b for Treatment of Pediatric Multiple Sclerosis," *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* 116, no. 6 (2016): 73–75, https://doi.org/10.17116/jnevro20161166173-75.

43. European Medicines Agency, "Drugs Approved for Multiple Sclerosis.", accessed 15 July, 2024, https://www.ema.europa.eu/en/search?search_api_fulltext=multiple%20sclerosis&f%5B0%5D=ema_search_custom_entity_bundle%3Aother&page=1.

44. E. Havrdova, D. Horakova, and I. Kovarova, "Alemtuzumab in the Treatment of Multiple Sclerosis: Key Clinical Trial Results and Considerations for Use," *Therapeutic Advances in Neurological Disorders* 8 (2015): 31–45.

45. R. Abolfazli, S. Pournourmohammadi, A. Shamshiri, and S. Samadzadeh, "Tolerability and Safety Profile of a New Brand-Generic Product of Glatiramer Acetate in Iranian Patients With Relapsing–Remitting Multiple Sclerosis: An Observational Cohort Study," *Current Therapeutic Research, Clinical and Experimental* 88 (2018): 47–51.

46. J. K. Alexander, R. Ariely, Y. Wu, et al., "Treatment Patterns Following Initiation of Generic Glatiramer Acetate Among Patients With Multiple Sclerosis From Two Large Real-World Databases in the United States," *Current Medical Research and Opinion* 37 (2021): 1323–1329.

47. D. V. Sazonov, L. A. Babenko, A. V. Yarmoschuk, and E. M. Didrikh, "An impact of glatiramer acetate (timexon) on the signs of neurodegeneration process in the neuronal layer of the retina in patients with relapsing–remitting multiple sclerosis," *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* 118 (2018): 25–30.

48. B. Greenberg, S. Hall, M. Grabner, S. Balu, X. Zhang, and D. Kantor, "Multiple Sclerosis Relapse Rates and Healthcare Costs of Two Versions of Glatiramer Acetate," *Current Medical Research and Opinion* 36 (2020): 1167–1175.

49. D. M. Hartung, K. A. Johnston, J. Geddes, and D. N. Bourdette, "Effect of Generic Glatiramer Acetate on Spending and Use of Drugs for Multiple Sclerosis," *Neurology* 94 (2020): e1407–e1414.

50. M. Castanheira, C. Ornaghi, and G. Siotis, "The Unexpected Consequences of Generic Entry," *Journal of Health Economics* 68 (2019): 102243.

51. A. Teeple, L. A. Ellis, L. Huff, et al., "Physician Attitudes About Nonmedical Switching to Biosimilars: Results From an Online Physician Survey in the United States," *Current Medical Research and Opinion* 35 (2019): 611–617.

52. I. Marín-Jiménez, M. J. Carrascosa, M. A. Guigini, and E. Monte-Boquet, "Knowledge, perceptions, attitude, barriers and facilitators of biosimilars use across specialty physicians and hospital pharmacists: a national survey," *Farmacia Hospitalaria* 45 (2021): 240–246.

53. K. Sarnola, M. Merikoski, J. Jyrkkä, and K. Hämeen-Anttila, "Physicians' Perceptions of the Uptake of Biosimilars: A Systematic Review," *BMJ Open* 10 (2020): e034183.

54. W. J. Brownlee, C. Wolf, H. P. Hartung, et al., "Use of Follow-On Disease-Modifying Treatments for Multiple Sclerosis: Consensus Recommendations," *Multiple Sclerosis* 28 (2022): 2177–2189.

55. C. Blandizzi, P. L. Meroni, and G. Lapadula, "Comparing Originator Biologics and Biosimilars: A Review of the Relevant Issues," *Clinical Therapeutics* 39 (2017): 1026–1039.

56. European Medicines Agency, "Statement on the Scientific Rationale Supporting Interchangeability of Biosimilar Medicine in the EU,", accessed April 3, 2024, https://www.ema.europa.eu/en/documents/public-statement/statement-scientific-rationale-supporting-interchangeability-biosimilar-medicines-eu_en.pdf.

57. G. Zanga, D. Caruso, E. Drzewiscki, M. Smietniansky, and Y. R. M. M. Esnaola, "Adherence to Treatment of Multiple Sclerosis in a Health Care Program," *Medicina (B Aires)* 81 (2021): 311–317.

58. S. B. Dusetzina, R. J. Besaw, C. C. Whitmore, et al., "Cost-Related Medication Nonadherence and Desire for Medication Cost Information Among Adults Aged 65 Years and Older in the US in 2022," *JAMA Network Open* 6 (2023): e2314211.

59. S. G. Morgan and A. Lee, "Cost-Related Non-adherence to Prescribed Medicines Among Older Adults: A Cross-Sectional Analysis of a Survey in 11 Developed Countries," *BMJ Open* 7 (2017): e014287.

60. K. W. Rohatgi, S. Humble, A. McQueen, et al., "Medication Adherence and Characteristics of Patients Who Spend Less on Basic Needs to Afford Medications," *Journal of American Board of Family Medicine* 34 (2021): 561–570.

61. J. Steinberg, Y. D. Fragoso, J. C. Duran Quiroz, et al., "Practical Issues Concerning the Approval and Use of Biosimilar Drugs for the Treatment of Multiple Sclerosis in Latin America," *Neurology and Therapy* 8 (2019): 207–214.

62. S. Gran-Ruaz, A. Mani, and S. O'Quinn, "An Overview of Biosimilars and Non-biologic Complex Drugs in Europe, the United States, and Canada and Their Relevance to Multiple Sclerosis," *Multiple Sclerosis* 23 (2017): 1824–1829.

63. B. S. Edgar, A. S. Cheifetz, S. M. Helfgott, et al., "Overcoming Barriers to Biosimilar Adoption: Real-World Perspectives From a National Payer and Provider Initiative," *Journal of Managed Care & Specialty Pharmacy* 27 (2021): 1129–1135.

64. H. Cohen, D. Beydoun, D. Chien, et al., "Awareness, Knowledge, and Perceptions of Biosimilars Among Specialty Physicians," *Advances in Therapy* 33 (2017): 2160–2172.

65. C. J. Edwards, J. Hercogova, H. Albrand, and A. Amiot, "Switching to Biosimilars: Current Perspectives in Immune-Mediated Inflammatory Diseases," *Expert Opinion on Biological Therapy* 19 (2019): 1001–1014.