MULTIPLE SCLEROSIS JOURNAL | MSJ

Supplement

The regulator's perspective: How should new therapies and follow-on products for MS be clinically evaluated in the future?

Multiple Sclerosis Journal

2016, Vol. 22(2S) 47–59

DOI: 10.1177/1352458516650744

Daan JA Crommelin, Karl Broich, Chris Holloway, Bianca Meesen, Jana Lizrova Preiningerova, Jean-Louis Prugnaud and Beatriz Silva-Lima

Abstract:

Background: Although there is still no cure for multiple sclerosis (MS), the introduction of several innovative drugs with modes of action different from that of the existing drug arsenal and the progress in monitoring disease progression by imaging and using biomarkers are currently causing a knowledge surge. This provides opportunities for improving patient disease management. New therapies are also under development and pose challenges to the regulatory bodies regarding the optimal design of clinical trials with more patient-focused clinical endpoints. Moreover, with the upcoming patent expiry of some of the key first-line MS treatments in Europe, regulatory bodies will also face the challenge of recommending marketing authorisation for generic and abridged versions based on appropriate requirements for demonstrating equality/similarity to the innovator's product.

Objective: The goal of this article is to improve the understanding of the relevant guidance documents of the European Medicines Agency (EMA) on clinical investigation of medicinal products and to highlight the issues that the agency will need to clarify regarding follow-on products of first-line MS treatments.

Conclusion: Today, it is clear that close collaboration between patients, healthcare professionals, regulatory bodies and industry is crucial for developing new safe and effective drugs, which satisfy the needs of MS patients.

Keywords: Biosimilars, follow-on products, generics, multiple sclerosis, non-biological complex drugs (NBCDs), safety

Date received: 15 April 2016; accepted: 23 April 2016

Correspondence to:
DJA Crommelin
Department of Pharmaceutics, Pharmaceutical Sciences, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Sciences, Utrecht University, Utrecht 3584 CG, The Netherlands.
D.J.A.Crommelin@uu.nl

Daan JA Crommelin
Department of Pharmaceutics, Pharmaceutical Sciences, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Sciences, Utrecht University, Utrecht, The Netherlands

Karl Broich
President and Head of the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Bonn, Germany

Chris Holloway
European Regulatory Consultant, Chief Scientific Officer of ERA Consulting GmbH, Walsrode, Germany

Bianca Meesen
Managing Director at Ismar Healthcare, Lier, Belgium

Jana Lizrova Preiningerova
Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University, Prague, Czech Republic

Jean-Louis Prugnaud
Expert Involved in the Development of Recommendations Related to Drug Registrations, Paris, France

Beatriz Silva-Lima
iMed.ULisboa, Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal

Introduction

Investment in research for new drugs for central nervous system (CNS) disorders is considerably lower than for other diseases.[1] This might be explained by several issues such as the lack of adapted pre-clinical models, problems to find the right dose for a given drug, the outsized and extended duration of the clinical trials, the high failure rate and (too) high regulatory requirements.[1] Therefore, in most cases, return on investment is considered to be poor. Multiple sclerosis (MS) as one of the most common diseases of the CNS is an exception. An impressive number of disease-modifying drugs (DMDs) to treat this disabling disorder have emerged over the past two decades.[2] Figure 1 shows the (relative) efficacy and safety of the present arsenal of DMDs in MS.

MS is a progressive inflammatory, demyelinating and neurodegenerative autoimmune disease of the CNS. It is the most common cause of neurological disability in young adults and affects approximately 630,000 people in Europe.[3] MS takes different forms, with new symptoms appearing in attacks (relapsing–remitting forms) and/or building up over time (progressive forms). Untreated MS patients usually progress and develop significant disability a few years from disease onset.

The understanding of the pathophysiology of MS has significantly improved in recent years. This has led to the development of many DMDs that aim to prevent or reduce the development of new lesions and relapses and/or delay disability progression in patients with relapsing–remitting MS.

Figure 1. MS therapeutic decision-making.[2]

To promote the introduction of safe and effective new MS treatments that better match the patient's needs, dialogue and cooperation between all stakeholders involved in MS must be encouraged. To that end, the Pan-European MS Multi-stakeholder Colloquia were organised in Brussels on 23–24 May 2014[4] and 15–16 May 2015.[5] The programmes developed by the chairs and scientific committee aimed at prioritising and defining actions needed to improve the quality of and access to care and treatment. The different stakeholders, including patients, healthcare professionals, regulators and payers presented their views in a series of sessions around specific topics. During the first Colloquium several interrelated 'Calls to Action'[6] on the European Union (EU), its member states and the research and global community were developed. The second Colloquium focused on developing innovative recommendations or 'Guidance Propositions' to address and refine these Calls to Action.

In this review, we will summarise the content of the presentations and discussions related to the regulatory perspective.

Marketing authorisation of new MS treatments is centrally assessed in Europe (Regulation (EC) No. 726/2004 of the European Parliament and of the Council) by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and involves considerations by expert regulators and healthcare professionals. The first part of this review will detail the main issues for the CHMP/EMA when recommending marketing authorisation for new MS treatments within the EU.

Although the prevalence of MS is relatively low, the economic impact of MS is significant due to its early onset, its progressive character and lifelong need for treatment. The availability of cheaper alternatives after patent expiry of the original products may contribute to increased access to treatments and/or a reduction in the cost rise of managing the disease. As some of the major first-line MS treatments are coming off patent, the CHMP/EMA will face the challenge of defining the appropriate requirements for (some) follow-on products to show a high degree of similarity, in order to safeguard the patients (and their physicians). The second part of this review will discuss how to deal with issues related to demonstration of comparability or similarity for small molecule drugs, biologicals and non-biological complex drugs (NBCDs) used in the management of MS.

Guideline on clinical investigation of medicinal products for the treatment of MS: update needed?

The guideline on clinical investigation of medicinal products for the treatment of MS provides an overview of all clinical requirements that should be fulfilled by an innovator's company when developing new MS treatments. The guideline criteria differ depending on the goal of the MS treatment (symptomatic relief,

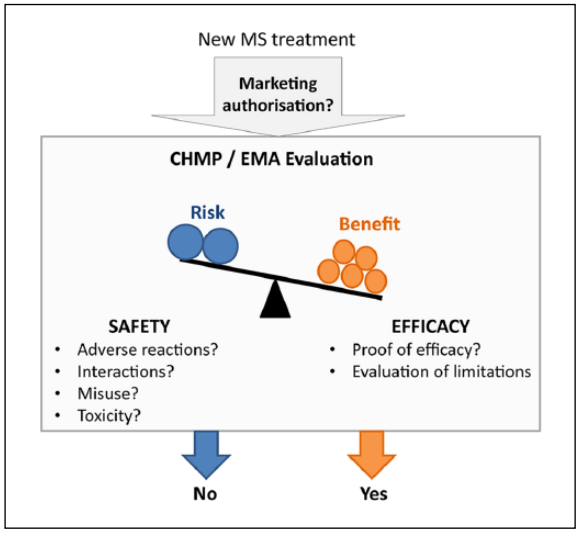

Figure 2. Evaluation of new MS treatment for marketing authorisation in Europe.

treatment of acute relapses or disease modification). The request for marketing authorisation of new MS treatments is then evaluated by the CHMP (Figure 2). This decision-making process is a benefit (efficacy)–risk (safety) assessment, to ensure approval of effective treatments. The benefits must outweigh the risks. The benefit considerations include proof of efficacy of the new MS treatment and evaluation of its limitations such as possible differences between populations and age groups or differential individual response. The risk evaluation focuses on adverse drug reactions and potential interactions, misuse and toxicity of the new MS treatment. Limitations are assessed by verifying the number of patients studied, the possible differences between populations and age groups, and the potential limited duration of active treatment.

Guideline on clinical investigation of medicinal products for the treatment of MS

The European guideline on clinical investigation of medicinal products for the treatment of MS was introduced in 1998 by the EMA and updated in 2006.[7] The first treatment goal in the guideline is the treatment of acute relapses. Any new MS treatment has to shorten their duration, reduce their severity and prevent their sequelae. The second goal is disease modification by preventing or modifying relapses, but also by preventing or delaying disability. The third goal is symptomatic improvement of residual disability.

However, with the remarkable improvement of imaging techniques and the development of biomarkers, as well as the launch of a large variety of drugs with innovative modes of action, it is obvious that the guideline needed to be updated. In May 2011, the EMA launched a Concept Paper to propose its revision.[8] A draft guideline was proposed in October 2012[9] followed by an EMA workshop in October 2013 to provide stakeholders with an opportunity to discuss and optimise the guideline.[10] The CHMP/EMA released the final guideline incorporating the key issues on clinical investigation of medicinal products for the treatment of MS in March 2015.[11] In the following sections, a number of key issues related to these guidelines will be briefly discussed.

Key issues for the clinical investigation of medicinal products for the treatment of MS

The use of placebo. There are several medicines available on the market, which effectively reduce the rate of relapses. From a regulatory point of view, for new treatments in MS, the preferred development approach would be to show superiority against placebo or an active comparator (i.e. first-line DMDs like interferon-beta (IFNβ) or glatiramer acetate (GA)).[12,13] However, this type of trial needs large numbers of patients for demonstrating improved efficacy over the reference treatment, which increases the development costs of any new drug. Therefore, a non-inferiority approach would also be acceptable, provided that assay sensitivity and a reasonable non-inferiority margin can be defined and adequately justified.[14] However, non-inferiority studies against first-line DMD products without an additional placebo arm are not considered sufficient, as their effect size regarding relapse rate is considered rather modest and any loss of efficacy would be close to the effect seen under placebo.[13]

Methods to assess the progression of disability. In addition to reducing time to relapse or relapse rate, the new MS treatment has to modify accumulation/progression of disability (whether or not this is related to a previous relapse). The main problem is how to assess the progression of disability.

The Expanded Disability Status Scale (EDSS) has been the most frequently used tool to monitor disability progression in MS.[15] It basically evaluates physical impairment on a scale from 0 (normal neurological examination) to 10 (death due to MS) (Figure 3). In patients with an EDSS $\leqslant$ 5, a 1-point change from baseline sustained for 3 months is usually considered as progression. Although it has been recognised for many years that the EDSS has several limitations, the EDSS is still recommended by health authorities to document disability progression in clinical trials as it

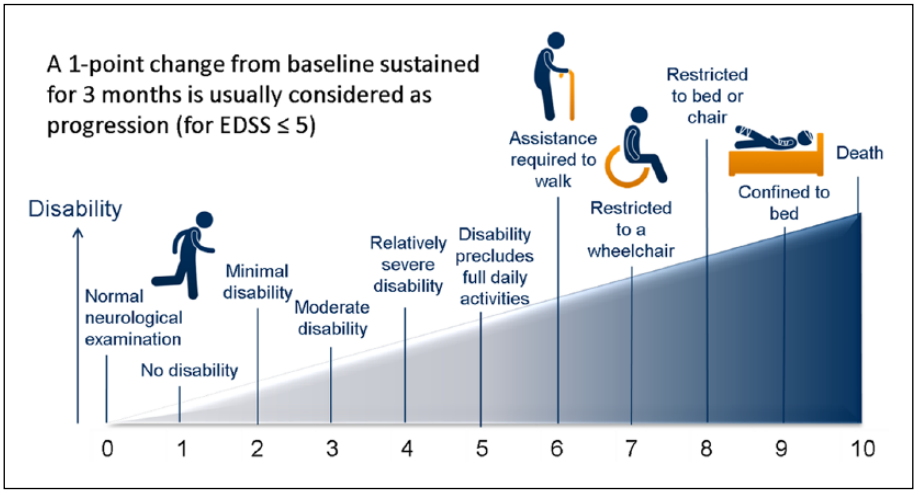

Figure 3. EDSS is the most frequently used tool to monitor disability progression in MS.[15]

facilitates comparisons with other studies and represents a robust outcome for health economists. The limitations include large inter- and intra-individual variability, excessive focus on capturing physical disability/mobility and no sensitivity to cognitive impairment. Moreover, because it is a non-linear ordinal scale, it is less sensitive to change in people with MS who have severe disability at baseline (EDSS ⩾ 4).

Alternatively, the three-part, standardised and quantitative Multiple Sclerosis Functional Composite (MSFC) assessment instrument could be used in clinical studies.[16] The MSFC measures various types of disability, that is, ambulation by the Timed 25-Foot Walk test (T25-FW), arm function by the 9-hole peg test (9HPT) and cognitive function by the Paced Auditory Serial Addition Test (PASAT). In addition, other tests, such as Sloan Low Contrast Visual Acuity test, Symbol Digit Modality Test (SDMT) or patient determined 12-Item MS Walking Scale (MSWS-12), can be utilised individually.

None of these aforementioned tools can perfectly quantify disability progression; hence, the EMA encourages the development of new instruments.

Patient-reported outcomes focussed on the expectations of patients. Whereas physicians focus on clinical outcomes such as relapse rate, disability progression, the impact on different magnetic resonance imaging (MRI) parameters or disease-free status when measuring treatment success, patients with MS are more concerned about the impact on outcomes such as cognition, fatigue and quality of life (QoL).[17] However, studies that tried to quantify the incidence of cognitive impairment in patients with MS showed large inconsistencies ranging from 5.5% of a cohort exhibiting cognitive impairment[18] to 59.7%.[19] The differences are probably due to the diverse methodology used to measure cognitive function. Therefore, reliable and validated measurement tools are needed to better evaluate cognitive impairment in patients with MS.

Today, none of the MS treatments target cognitive impairment and/or fatigue. Nevertheless, it is recognised that fatigue and cognitive dysfunction contribute to the QoL of patients with MS.[20] The EMA supports the use of QoL assessment in patients with chronic illnesses.[21] Therefore, QoL assessment should be better understood, investigated and validated for use in MS.

The use of biomarkers as an outcome in clinical trials. Generally, the EMA encourages the development and use of biomarkers because they can increase the understanding of the biology of a disease or the effects of medicinal products and they can help in the development of better diagnostics and medicinal products. Biomarkers can also improve the methodology of clinical trials and provide information on sub-populations of patients that might respond (better) to a treatment or are (more) susceptible to adverse drug reactions (individualised medicine). This could reduce the trial length/size, treatment costs and healthcare burden on payers and society.

In MS, MRI scans are currently considered to be the most interesting potential biomarker for predicting long-term disability progression.[22–24] However, as none of the MRI variables have been adequately validated as surrogate endpoint for clinical outcome, MRI

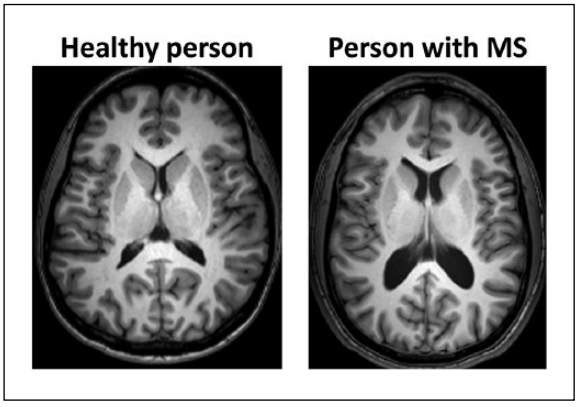

Figure 4. Whole brain atrophy at MRI scans seems to predict long-term disability progression. Whole brain atrophy reflects the net effect of brain tissue damage.[26]

outcome measurements are to date not accepted by regulators as primary endpoint in pivotal studies for new medical agents. Nevertheless, several studies have shown that whole brain atrophy at MRI scans, which reflects the net effect of brain tissue damage, can predict long-term disability progression[25] (Figure 4). Unfortunately, although whole brain atrophy is a sensitive MRI measure to predict long-term disability progression, there are currently several limitations to its use.[27] In order to overcome these limitations, it is essential to develop a protocol for standardisation of this MRI measurement.[28] In addition, it should be evaluated how much change in, for example, whole brain atrophy is needed to induce a percentage change in disability outcome. This also applies to other more advanced imaging techniques such as magnetisation transfer ratio (MTR), double inversion recovery (DIR) and optical coherence tomography (OCT) imaging to assess lesion volume, cortical lesions and neurodegeneration. Research into other biomarkers, for example in body (cerebrospinal) fluids or genetic biomarkers, which may predict long-term disability progression and individual response to treatment, should also receive high priority.[28]

Safety. Given that MS is a chronic disease and an established drug may be used over a long period of time, long-term safety data (>2 years) in a large and representative group of MS patients is required at the time for application of marketing authorisation. Depending on the safety of the product, additional post-marketing utilisation studies and safety registries may be needed.

The majority of drugs developed for the treatment of MS target the immune system and thus potentially raise serious safety concerns such as infections, malignancies and autoimmune disorders. Special attention should be given to assess potential adverse events that are typical for a class of drugs (e.g. neutralising antibodies against biological products or depression and seizures for interferons) and to the occurrence of neurological exacerbations or adverse events. Also the effect of withdrawal of the drug should be systematically assessed by clinical and/or MRI monitoring over a sufficient period of time after discontinuation.

In patients with severe disease activity at onset, characterised by frequent relapses and the accumulation of focal lesions visible on the MRI scan, induction therapy with a powerful immunosuppressant, such as alemtuzumab[29] may be considered in order 'to hit hard and early'.

Alemtuzumab is perceived as more effective than other DMD (e.g. IFNβ-1a),[30] but this comes at the price of several serious adverse events.[31] Therefore, the use of alemtuzumab requires monitoring for infusion reactions and prophylaxis for herpes virus infections and *Pneumocystis jirovecii pneumonia* (PCP) during treatment and for several weeks after treatment. Prolonged surveillance for bone marrow suppression, infections and autoimmune disorders such as idiopathic thrombocytopenic purpura is also necessary.

It is noteworthy that the CHMP assessment of alemtuzumab, for which market authorisation was granted in 2013, was performed differently than for prior approved DMDs (e.g. fingolimod).

Accelerate access to treatment. The adaptive licensing approach is part of the attempts of the EMA to improve quick access for patients with indications of high unmet medical need and might be considered for new MS treatments[32] (Figure 5). This process starts with 'conditional initial approval', that is, the early authorisation of the medicine in a controlled patient population, followed by phases of collecting evidence and adaptations of the marketing authorisation to expand the access of the medicine to broader patient populations.

The goal of this approach would be to faster expand the expected positive impact of new MS treatments while maintaining a balance between timely access for patients and the need to provide sufficient information on the benefits and risks of the new treatments.

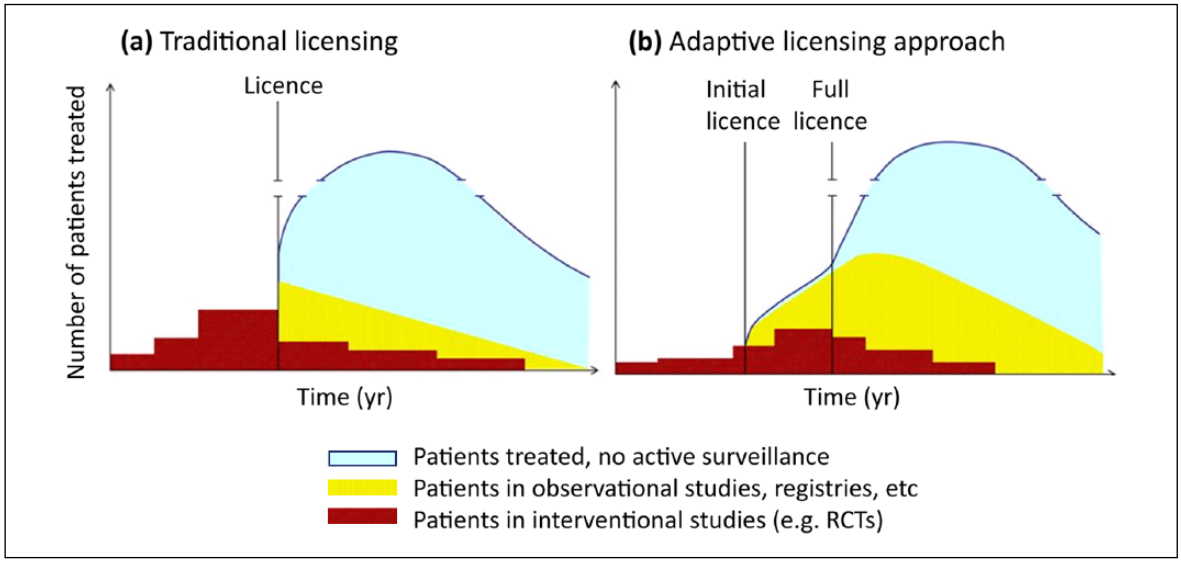

Figure 5. Patients exposure to the new drug and time to marketing authorisation granting in traditional licencing:[32] (a) after licence, treatment population grows quickly but treatment experience does not contribute to evidence generation, compared with the adaptive licensing approach and (b) after initial licence, treatment population grows slowly (due to restrictions) but treatment experience is captured to contribute to evidence generation.
RCTs: randomised controlled trials.

How to deal with issues for demonstrating comparability or similarity for small molecule drugs, biologicals and NBCDs used in the management of MS?

With the patent expiry of some of the key first-line MS treatments in Europe, the CHMP will face the challenge of advising on providing marketing authorisation to follow-on products of the original medicinal product.

Follow-on products of small molecule drugs

In Europe, regulatory bodies are encouraged to provide rapid access to the market for lower-priced copies of original medicinal products after patent expiry in order to reduce healthcare costs. To this end, the CHMP has elaborated abbreviated regulatory pathways based on demonstration of pharmaceutical equivalence (i.e. identical active substance, dosage form and route of administration) and bio-equivalence (i.e. comparable pharmacokinetics) established in a small healthy volunteer study. These abbreviated regulatory pathways do not require formal clinical efficacy and/or safety studies.

The classical generic approval approach has been successful for many well-defined, small, low-molecular weight drugs, where physicochemical analytical testing can fully characterise the product (e.g. corticosteroids) (Figure 6).

Follow-on products of biological drugs

Rapid advances in drug development resulted in the discovery of biological substances as medicinal products (commonly known as biologicals). Biologicals are produced by or extracted from living organisms and exhibit high molecular complexity compared to small molecule drugs.[33] Full physicochemical characterisation to establish equality of structure of these complex molecules (in particular for the larger proteins) is not possible, even with state-of-the-art analytical techniques. Furthermore, the product attributes depend, in no small measure, on the manufacturing process. Differences in molecular building blocks and three-dimensional structure, impurities and/or degradation products can have significant impact on the therapeutic effect and these may be affected by the specifics of the manufacturing process. Therefore, the 'classical' equivalence principle as accepted for small molecule drugs cannot be applied for biologicals (e.g. IFNβ)[33] (Figure 6).

The fact that follow-on products of biologicals might act differently than the original biological product led to the introduction of the CHMP guideline document in 2005 with general requirements for a similar biological product (biosimilar)[34] that was updated in 2014.[35] The current revision recommends a stepwise approach for the design of non-clinical and clinical studies,[35] whereas quality issues relevant for demonstration of biosimilar comparability are addressed in a

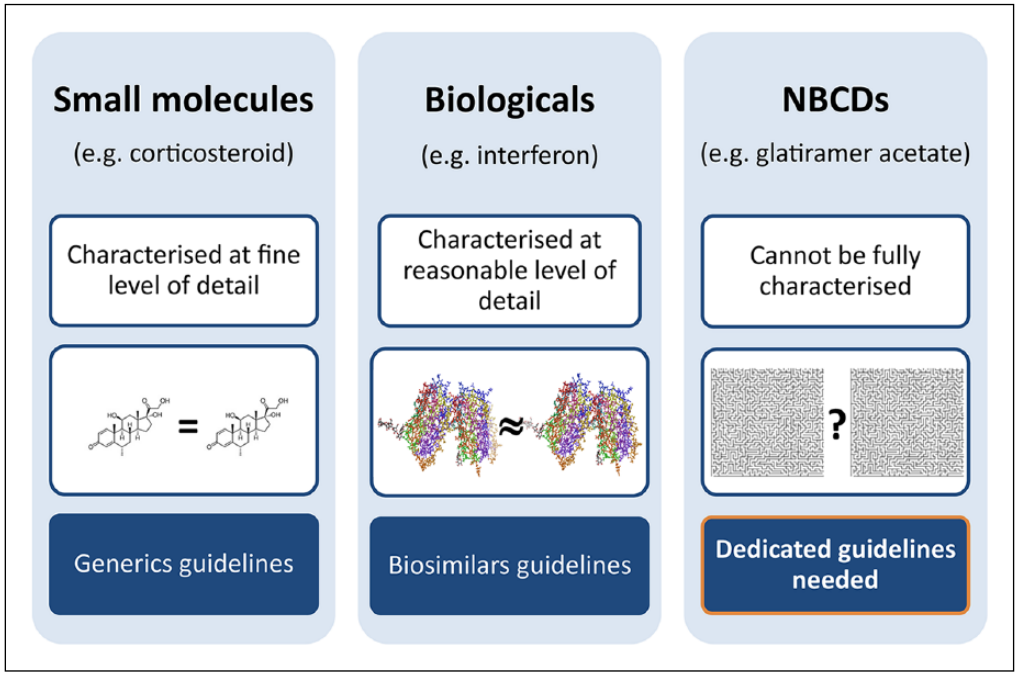

Figure 6. Three categories of drugs with reference to the guidelines needed for demonstration of similarity.
NBCDs: non-biological complex drugs.

Table 1. Product-specific biosimilar guidelines by the EMA.

Similar biological medicinal products	Guideline reference number	Effective date
Containing recombinant follicle-stimulating hormone	CHMP/BMWP/671292/2010	1 September 2013
Containing interferon-beta	CHMP/BMWP/652000/20100	1 September 2013
Containing monoclonal antibodies: non-clinical and clinical issues	EMA/CHMP/BMWP/403543/2010	1 December 2012
Containing recombinant erythropoietin	EMEA/CHMP/BMWP/301636/08	30 September 2010
Containing low-molecular-weight heparins	EMEA/CHMP/BMWP/118264/2007	October 2009
Containing recombinant interferon-alpha	EMEA/CHMP/BMWP/102046/2006	April 2009
Containing recombinant granulocyte-colony-stimulating factor	EMEA/CHMP/BMWP/31329/2005	June 2006
Containing somatropin	EMEA/CHMP/BMWP/94528/2005	June 2006
Containing recombinant human insulin	EMEA/CHMP/BMWP/32775/2005	June 2006

EMA: European Medicines Agency.

separate guideline.[36] In addition, the advances as well as the still existing limitations of methods and techniques currently available for the full characterisation of biologicals have prompted the CHMP to establish a number of guidelines relevant to quality, non-clinical and clinical issues to be addressed in the development programmes of specific biosimilar medicinal products (Table 1).

In conclusion, the development of biosimilars is currently appropriately regulated in the EU. Hopefully, the patient will soon gain access to high quality but cheaper biologicals, be it the innovator or a biosimilar version, for the treatment of MS.

Follow-on products of NBCDs

A class of medicinal products, which falls outside both categories described above, are the so-called NBCDs (e.g. iron–sucrose complex, liposomal formulations and GA)[37] (Figure 6). The active substance of NBCDs is not a homogeneous molecule, but rather

a heterogeneous mixture consisting of different closely related and often (polymer-based) nanoparticulate structures. It is very hard to fully quantify/characterise these substances by state-of-the-art physicochemical analytical methods.[38] It is also unknown which structural elements relate to the therapeutic benefits and risks. The composition, quality and *in vivo* effects of NBCDs are highly dependent on the manufacturing processes of both the active ingredient and the formulation.[39]

Compared with biologicals, the regulatory basis for NBCDs is not yet sufficiently defined as dedicated guidelines are not available. However, the development of such guidelines is crucial, as illustrated by the following two examples of NBCDs.

Example 1: iron–sucrose complexes. Iron–sucrose complexes are medicinal products used to replenish iron stores in patients with iron deficiency. A follow-on product showing similar physicochemical properties as the reference medicinal product, Venofer®, was approved as generic version in several European countries.[40] However, differences between the two products were observed in clinical practice. A well-controlled haemodialysis population in France destabilised when supplemented with the follow-on instead of the reference product, with the necessity for higher doses of iron–sucrose and erythropoietin, an increased mean number of days outside of the target haemoglobin range and increased costs for managing anaemia.[41] It was concluded that the follow-on product was not therapeutically equivalent to the reference iron–sucrose complex.[41] In addition, it was shown that the reference iron–sucrose preparation and its follow-on products had different effects on nitrosative stress, apoptosis, oxidative stress and biochemical and inflammatory markers in rats.[42]

Therefore, on March 2011, the CHMP adopted a Reflection Paper on non-clinical studies for generic nanoparticle iron medicinal product applications.[43] This Reflection paper described the view of the CHMP on the type of non-clinical studies necessary to support the approval of follow-on products of iron medicinal products. Among other things, the CHMP concluded that physicochemical characterisation of the drug substance and pharmacokinetics studies may not be sufficient to ensure 'essential similarity' for iron medicinal products.

Example 2: GA. GA has immunomodulatory effects on innate and acquired immunity and is indicated for the treatment of patients with relapsing–remitting MS.[44] GA is synthesised from four amino acids in a fixed ratio. It is not a single molecular entity but a heterogeneous mixture of potentially millions of distinct, synthetic polypeptides of varying lengths, some containing up to 200 amino acids, some of these polymers in aggregated form, with a structural complexity exceeding that of recombinant proteins.[45] Until now, it is not possible to separate and identify the pure components, not even when using advanced multidimensional separation techniques.[45]

The complexity of GA is explained by a number of aspects.[45,46] The active moieties in GA have not been identified; the mechanism of action is not fully understood; pharmacokinetic testing is not indicative of GA bioavailability; pharmacodynamic testing is not indicative of therapeutic activity as there are no biomarkers available as surrogate measures of efficacy; and small changes in the GA mixture can change its immunogenicity profile.

For instance, protiramer (or TV-5010), which was developed some years ago as a second-generation, more potent glatiramoid with a slightly different molecular weight distribution but a similar amino acid ratio, was shown to be more potent than GA in a mouse inflammation model of MS, with no toxicity in short-term (13 weeks) rat studies. This led to the conduct of phase II studies in patients with MS, which showed good safety and tolerability in two short-term (36 weeks) clinical studies.[47] In contrast, protiramer was found to be toxic (increased mortality) in longer term safety studies in monkeys (52 weeks) and rats (26 weeks)[48] and subsequently clinical development was stopped for that reason.

While a follow-on product of GA may appear to be similar using conventional analytical methods, in-depth characterisation can reveal differences. This is the case for several follow-on products commercialised following a national procedure[49] (Table 2).

For example, the three follow-on products Glatimer®, Probioglat® and Escadra® show significant differences in charge distribution by capillary isoelectric focusing (CIEF) and aggregate size in colloidal dispersions by dynamic light scattering (DLS) when compared with reference GA, whereas batches of reference GA fall within the microheterogeneity range.[49] Moreover, advanced gene-expression analyses have shown important differences in the expression of specific pro-inflammatory genes and immune cells (Figure 7(a)).[50,51] One example is the CD14 gene, which is expressed in abundance on the surface of mature monocytes and in trace amounts on granulocytes, but not on other hematopoietic cells.[52] CD14 is known to

Table 2. Glatiramer acetate 20 mg daily subcutaneous injection and its follow-on products.

Product		Company	Market
Original GA product	Copaxone®	Teva	57 countries worldwide
Follow-on product	Glatimer®	Natco	India
	Probioglat®	Probiomed	Mexico
	Escadra®	Raffo	Argentina
	Glatopa®	Sandoz/Momenta	United States

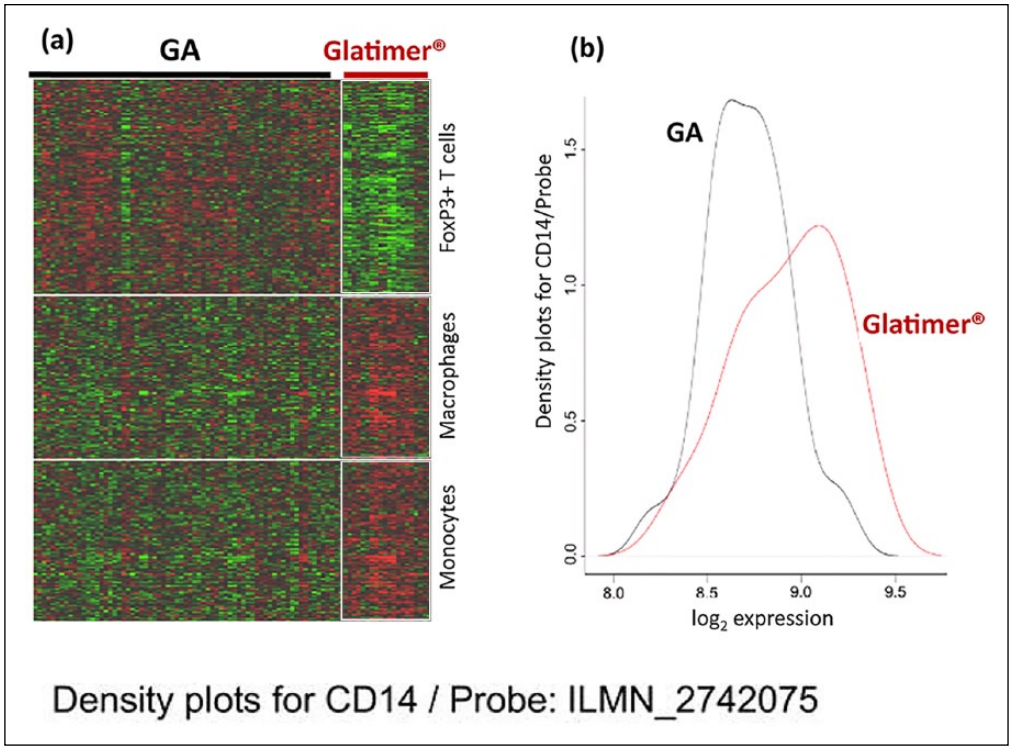

Figure 7. (a) The heat map representing the relative expression of genes in GA and Glatimer®-activated samples. Each of the rows within the Treg, macrophage and monocyte sections represents a gene with a high cell-type specificity score for each cell type. Overall, GA induces higher expression of Treg-associated genes than Glatimer®, while Glatimer® induces higher expression of macrophage and monocyte-associated genes than GA.[50] (b) Glatimer® induces significantly higher expression of CD14 ($p = 0.0203$).[50]
The box for the T cells with more green/white included represents low expression, whereas the boxes for the macrophaes and monocytes with more red/less white included represents high expression.

enhance the inflammatory response.[52] Higher CD14 expression levels are found in Glatimer®-treated samples (Figure 7(b)).[50] Probioglat®, like Glatimer®, significantly up-regulates CD14, compared with reference GA.[51] Gene expression findings raise concerns that the follow-on products may not be biologically and clinically equivalent to GA. In particular, significant up-regulation of pro-inflammatory genes is highly undesirable in MS.

Perhaps the most worrying are the reports of patients experiencing serious adverse events after the introduction of follow-on products of GA outside the EU. Some of the most serious reports come from one of the biggest hospitals of the Mexican Institute of Social Security, the Hospital la Raza (Mexico City), which regularly follows 232 patients with MS. In total, 65 patients were treated with both Probioglat® and Copaxone® since January 2013. They report breakthrough relapses within weeks or months of exposure to Probioglat® and symptoms that include severe pain, increase in injection-site reactions, erythema and diffuse flush, pruritus and chest pain (consistent with immediate post-injection reaction). These observations were confirmed by healthcare providers. Many of these conditions led

to hospitalisation and relapse-related hospitalisations increased by 200% in 2013.[53]

A citizens petition, bringing the aforementioned differences between Copaxone® and its follow-on products under attention and requesting that the Food and Drug Administration (FDA) refrains from approving any abbreviated new drug application referencing Copaxone® until certain conditions are met, was recently denied.[54] Furthermore, the FDA approved Glatopa®, as a first follow-on of GA for US launch in April 2015, based on guidelines for generic drugs. Although the complex nature of GA was taken into account for proving physiochemical sameness, no *in vivo* bioequivalence studies were deemed necessary.[54]

Nevertheless, the non-clinical and clinical examples summarised before highlight the need for a clear regulatory pathway and appropriate guidelines for the development and approval of follow-on products to NBCDs such as GA by EMA. As with biosimilar products, NBCDs' characteristics are inexorably linked to their production process; therefore, similarity cannot be assumed for their follow-on product(s). An extensive analytical characterisation of a follow-on product complemented with a clinical trial programme is needed to ascertain efficacious and safe use in clinical practice.

Conclusion

In the past 30 years, new and effective therapies have been developed for the treatment of MS. The new CHMP guideline on clinical investigation of medicinal products for the treatment of MS, that came into effect on 01 October 2015, considered these developments (e.g. better fits the patient needs). While relapses and the physical disability aspect of MS are of great importance, it is now well recognised that it does not reflect all facets that patients consider important in their life. Research to develop, evaluate and validate new assessment tools to better capture patient-related disability, fatigue, cognitive function and QoL as well as to find and validate imaging and body fluid biomarkers, which can predict long-term disability progression, is strongly encouraged.

The encouragement of healthcare professionals to substitute or interchange original products with generic products has led to cost savings. The availability of lower-priced follow-on products to first-line DMDs also may reduce the direct costs associated with MS. The September 2013 guideline for the development of biosimilar medicinal products containing IFNβ will hopefully encourage the development of IFNβ biosimilars.

NBCDs, such as GA, which present great complexity in terms of molecular characteristics, raise specific challenges during their development, manufacturing, clinical testing and quality control. Three follow-on products (Glatimer®, Probioglat® and Escadra®) were approved through national procedures outside of highly regulated jurisdictions, whereas the FDA recently approved the first follow-on product (Glatopa®) for US launch in April 2015. All approvals were based on guidelines for generic drugs (equivalence principle). However, in our and also other experts opinion,[55] this strategy carries risks for a follow-on product of this NBCD because relevant differences may be missed by physicochemical and biological characterisation only. It is therefore crucial to have dedicated clearly defined regulatory pathways for NBCDs, including clear directions for the design of clinical trials, to ensure the efficacy and safety of these follow-on NBCDs.[49]

Acknowledgements

The authors would like to thank Ismar Healthcare, Lier, Belgium for providing assistance with the writing of the manuscript based on the content of the presentations given at the Colloquium and the outcome of the related discussions and voting polls. This was supported by Teva Pharmaceuticals Europe. Karl Broich explicitly indicates that his contribution reflects his personal opinion as an expert in regulatory affairs and not that of the BfArM or of the CHMP/EMA.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Daan J.A. Crommelin received honoraria or consultation fees from Merck USA, Vifor, Teva, HAL allergy and venture capital companies. Karl Broich is Vice President and Head of BfArM, Bonn, Germany, Chair of the Central Nervous System Working Party (CNSWP) of the EMA, London, UK. He has no conflicts of interest, and ideas presented reflect personal views and cannot be considered as official statements of EMA or BfArM. Chris Holloway received honoraria or consultation fees from Teva Pharmaceuticals. Jana Lizrova Preiningerova received grants/research supports from Czech grant agency NT 13239-4 and Biogen Idec, and honoraria or consultation fees from Novartis, Biogen Idec and Teva. Jean-Louis Prugnaud received honoraria or consultation fees from Imaxio, Sanofi, Roche and Doliage.

Beatriz Silva-Lima received support for Colloquium participation sponsored by Teva Pharmaceuticals. Bianca Meesen is Managing Director of Ismar Healthcare who received support from Teva Pharmaceuticals Europe for facilitating the organisation of the Colloquium and proving writing assistance.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Teva Pharmaceuticals Europe.

References

1. Mattke S, Taylor EA, Hunter LE, et al. The new neglected diseases? Policy interventions are needed to encourage CNS drugs development. *RAND,* 2013, pp. 1–14.
2. Hauser SL, Chan JR and Oksenberg JR. Multiple sclerosis: Prospects and promise. *Ann Neurol* 2013; 74: 317–327.
3. Kobelt G, Berg J, Lindgren P, et al. Costs and quality of life of patients with multiple sclerosis in Europe. *J Neurol Neurosurg Psychiatry* 2006; 77: 918–926.
4. The first Pan-European multiple sclerosis multi-stakeholder colloquium: Exploring opportunities and challenges for improving multiple sclerosis management. Agenda, http://2014.ms-colloquium.org/programme (2014, accessed 3 December 2015).
5. The second Pan-European multiple sclerosis multi-stakeholder colloquium: Accelerating adoption of innovation for better care. Agenda, http://ms-colloquium.org/programme (2015, accessed 3 December 2015).
6. The Pan-European multiple sclerosis multi-stakeholder colloquia. Calls to action, https://dl.dropboxusercontent.com/u/7697080/MS%20Colloquium%202015/Calll_to_action2015.pdf (2015, accessed 3 December 2015).
7. CPMP/EWP/561/98. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. *EMEA*, 2006, pp. 1–12.
8. EMA/CHMP/CNSWP/257565/2011. Concept paper on the need for revision of guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. *EMA*, 2011, pp. 1–3.
9. EMA/CHMP/771815/2011. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. *EMA*, 2012, pp. 1–19.
10. EMA/576938/2013. Workshop on multiple sclerosis 17 October 2013. *EMA*, 2013, pp. 1–12.
11. EMA/CHMP/771815/2011. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. *EMA*, 2015, pp. 1–20.
12. Polman CH, Reingold SC, Barkhof F, et al. Ethics of placebo-controlled clinical trials in multiple sclerosis: A reassessment. *Neurology* 2008; 70: 1134–1140.
13. Balabanov P, Haas M, Elferink A, et al. Addressing the regulatory and scientific challenges in multiple sclerosis – A statement from the EU regulators. *Mult Scler* 2014; 20: 1282–1287.
14. Lesaffre E. Superiority, equivalence, and non-inferiority trials. *Bull NYU Hosp Jt Dis* 2008; 66: 150–154.
15. Cohen JA, Reingold SC, Polman CH, et al. Disability outcome measures in multiple sclerosis clinical trials: Current status and future prospects. *Lancet Neurol* 2012; 11: 467–476.
16. Cutter GR, Baier ML, Rudick RA, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain* 1999; 122(Pt 5): 871–882.
17. Rothwell PM, McDowell Z, Wong CK, et al. Doctors and patients don't agree: Cross sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis. *BMJ* 1997; 314: 1580–1583.
18. Weinges-Evers N, Brandt AU, Bock M, et al. Correlation of self-assessed fatigue and alertness in multiple sclerosis. *Mult Scler* 2010; 16: 1134–1140.
19. Deloire MSA, Bonnet MC, Salort E, et al. How to detect cognitive dysfunction at early stages of multiple sclerosis? *Mult Scler* 2006; 12: 445–452.
20. Baumstarck K, Pelletier J, Butzkueven H, et al. Health-related quality of life as an independent predictor of long-term disability for patients with relapsing-remitting multiple sclerosis. *Eur J Neurol* 2013; 20: 907–914.
21. EMEA/CHMP/EWP/139391/2004. Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. *EMEA*, 2005, pp. 1–5.
22. Filippi M and Agosta F. Imaging biomarkers in multiple sclerosis. *J Magn Reson Imaging* 2010; 31: 770–788.
23. Filippi M, Preziosa P, Copetti M, et al. Gray matter damage predicts the accumulation of disability 13 years later in MS. *Neurology* 2013; 81: 1759–1767.
24. Agosta F, Rovaris M, Pagani E, et al. Magnetization transfer MRI metrics predict the accumulation of

disability 8 years later in patients with multiple sclerosis. *Brain* 2006; 129: 2620–2627.

25. Jacobsen C, Hagemeier J, Myhr KM, et al. Brain atrophy and disability progression in multiple sclerosis patients: A 10-year follow-up study. *J Neurol Neurosurg Psychiatry* 2014; 85: 1109–1115.
26. Fisher E, Rudick RA, Simon JH, et al. Eight-year follow-up study of brain atrophy in patients with MS. *Neurology* 2002; 59: 1412–1420.
27. Lukas C, Sombekke MH, Bellenberg B, et al. Relevance of spinal cord abnormalities to clinical disability in multiple sclerosis: MR imaging findings in a large cohort of patients. *Radiology* 2013; 269: 542–552.
28. Vermersch P, Berger T, Gold R, et al. The clinical perspective: How to personalise treatment in MS and how may biomarkers including imaging contribute to this? *Mult Scler* 2016; S2: 18–33.
29. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: A randomised controlled phase 3 trial. *Lancet* 2012; 380: 1829–1839.
30. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 clinical trial. *Neurology* 2012; 78: 1069–1078.
31. Costelloe L, Jones J and Coles A. Secondary autoimmune diseases following alemtuzumab therapy for multiple sclerosis. *Expert Rev Neurother* 2012; 12: 335–341.
32. Eichler HG, Oye K, Baird LG, et al. Adaptive licensing: Taking the next step in the evolution of drug approval. *Clin Pharmacol Ther* 2012; 91: 426–437.
33. Crommelin D, Bermejo T, Bissig M, et al. Pharmaceutical evaluation of biosimilars: Important differences from generic low-molecular-weight pharmaceuticals. *EJHP-S* 2005; 11: 11–17.
34. CHMP/437/04. Guideline on similar biological medicinal products. *EMEA*, 2005, pp. 1–7.
35. EMEA/CHMP/BMWP/42832/2005. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues. *EMA*, 2014, pp. 1–13.
36. EMA/CHMP/BWP/247713/2012. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1). *EMA*, 2014, pp. 1–9.
37. Schellekens H, Klinger E, Mühlebach S, et al. The therapeutic equivalence of complex drugs. *Regul Toxicol Pharmacol* 2011; 59: 176–183.
38. Crommelin DJA, de Vlieger JSB, Weinstein V, et al. Different pharmaceutical products need similar terminology. *AAPS J* 2014; 16: 11–14.
39. Borchard G, Flühmann B and Mühlebach S. Nanoparticle iron medicinal products – Requirements for approval of intended copies of non-biological complex drugs (NBCD) and the importance of clinical comparative studies. *Regul Toxicol Pharmacol* 2012; 64: 324–328.
40. The European commission implementing decision concerning, in the framework of Article 31 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisations of 'Iron containing intravenous medicinal products', medicinal products for human use, http://ec.europa.eu/health/documents/community-register/2013/20130913126618/dec_126618_en.pdf (2015, accessed 3 December 2015).
41. Rottembourg J, Kadri A, Leonard E, et al. Do two intravenous iron sucrose preparations have the same efficacy? *Nephrol Dial Transplant* 2011; 26: 3262–3267.
42. Clark C. Are all parenteral iron sucrose preparations identical or just similar? *Hospital Pharmacy Europe*, October 2011, vol. 58, pp. 1–8.
43. EMA/CHMP/SWP/100094/2011. Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications. *EMA*, 2011, pp. 1–5.
44. Aharoni R. The mechanism of action of glatiramer acetate in multiple sclerosis and beyond. *Autoimmun Rev* 2013; 12: 543–553.
45. Varkony H, Weinstein V, Klinger E, et al. The glatiramoid class of immunomodulator drugs. *Expert Opin Pharmacother* 2009; 10: 657–668.
46. Johnson KP. Glatiramer acetate and the glatiramoid class of immunomodulator drugs in multiple sclerosis: An update. *Expert Opin Drug Metab Toxicol* 2010; 6: 643–660.
47. De Stefano N, Filippi M, Confavreux C, et al. The results of two multicenter, open-label studies assessing efficacy, tolerability and safety of protiramer, a high molecular weight synthetic copolymeric mixture, in patients with relapsing-remitting multiple sclerosis. *Mult Scler* 2009; 15: 238–243.
48. Ramot Y, Rosenstock M, Klinger E, et al. Comparative long-term preclinical safety evaluation of two glatiramoid compounds (glatiramer Acetate, Copaxone(R), and TV-5010, protiramer) in rats and monkeys. *Toxicol Pathol* 2012; 40: 40–54.

49. Crommelin DJA, Shah VP, Klebovich I, et al. The similarity question for biologicals and non-biological complex drugs. *Eur J Pharm Sci* 2015; 76: 10–17.
50. Towfic F, Funt JM, Fowler KD, et al. Comparing the biological impact of glatiramer acetate with the biological impact of a generic. *PLoS ONE* 2014; 9: e83757.
51. Kolitz S, Hasson T, Towfic F, et al. Gene expression studies of a human monocyte cell line identify dissimilarities between differently manufactured glatiramoids. *Sci Rep* 2015; 5: 10191.
52. Simmons DL, Tan S, Tenen DG, et al. Monocyte antigen CD14 is a phospholipid anchored membrane protein. *Blood* 1989; 73: 284–289.
53. FDA 2014-P-0933. Citizens petition requesting that FDA refrain from approving any abbreviated new drug application referencing Copaxone® until certain conditions are met, FDA 2014, pp. 1–132, http://www.regulations.gov/#!documentDetail;D=FDA-2014-P-0933-0001 (2014, accessed 3 December 2015).
54. FDA 2015-P1050. Citizens petition denial letter from CDER to Teva Pharmaceuticals, FDA 2015, pp. 1–43, http://www.noticeandcomment.com/Citizen-Petition-Denial-Letter-From-CDER-to-Teva-Pharmaceuticals-fn-259296.aspx (2015, accessed 3 December 2015).
55. Carrá A, Macias Islas MA, Tarulla A, et al. Biological and nonbiological complex drugs for multiple sclerosis in Latin America: Regulations and risk management. *Expert Rev Neurother* 2015; 15: 597–600.