

## Recombinant G-CSF products and what pharmacists need to know

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### ABSTRACT

**Study objectives:** To review pharmaceutical, clinical and quality issues of the innovator drug product and biosimilars containing recombinant granulocyte colony-stimulating factor (rhG-CSF) as an active substance.

**Methods:** A literature review of the currently available data in terms of quality, safety and efficacy.

**Results:** European Medicines Agency (EMA) has issued specific guidelines for the approval of biosimilars. A full quality (chemistry, manufacturing, controls) dossier and the results of non-clinical and clinical comparability studies are to be presented. In accordance with these guidelines, seven rhG-CSF biosimilars, referring to three different products, have gained market authorisation in the EU. Similarity in terms of quality, safety and efficacy to the reference product (Amgen filgrastim, Neupogen) are indicated in the European public assessment reports. However, there are points to consider when switching from the innovator product to a filgrastim biosimilar or from one filgrastim biosimilar to another. These are extrapolated indications, pharmacovigilance programmes and post-marketing safety as well as differences in handling and dosage forms.

**Conclusion:** Although EMA has developed robust regulatory requirements for the approval procedure of biosimilars there are open questions concerning extrapolated indications, pharmacovigilance, INN-naming, labelling, and substitution on pharmacy level. Therefore, clinicians and pharmacists should consider critical issues regarding the manufacture, formulation, supply, safety and tolerability of products in order to make informed decisions about the use of biosimilar filgrastim.

### KEYWORDS

Biosimilar, filgrastim, manufacturing process, quality, recombinant human granulocyte colony-stimulating factor (rhG-CSF)

### INTRODUCTION

Biopharmaceuticals are biological medicinal products derived from recombinant DNA (rh-DNA, recombinant human form) and expressed by genetically engineered organisms to produce the target therapeutic proteins in large quantities. During the last three decades, many biopharmaceuticals, including cytokines like haematopoietic growth factors (HGFs), interferons, and interleukins, have received marketing authorisation throughout the world. HGFs stimulate the proliferation, differentiation and function of haematopoietic cells. Recombinant human erythropoietin and granulocyte colony-stimulating factor (rhG-CSF) belong to the early biopharmaceuticals launched in Europe. As patents of products such as epoetin alpha and filgrastim (rhG-CSF) have already expired in the EU, so-called biosimilars ('similar' biological medicinal products) of these

products are currently approved by the EMA. The term biosimilar was defined by EMA along with the implementation of a specific regulatory framework for the marketing authorisation of these products [1]. A biosimilar is by definition not identical to the innovator product, but only similar. Subtle differences may exist between various products. However this similarity allows for cross-reference to data generated with the innovator (reference) product in the biosimilar application for marketing authorisation. Today the key question considered by the regulatory authorities and healthcare professionals is: How similar is similar enough?

### RECOMBINANT G-CSF BIOPHARMACEUTICALS

Human G-CSF is a single polypeptide chain protein of 174 amino acids with O-glycosylation at one threonine residue (MW 18 kDa, carbohydrate moiety 4% of total weight). It contains one free cysteinyl residue and two disulphide bonds. Cellular sources of G-CSF are monocytes, fibroblasts and endothelial cells. The physiological role of G-CSF is to maintain neutrophil production during steady-state conditions and to increase production during acute situations such as infection [2]. Effects of G-CSF on the target cells (granulocyte progenitors, mature neutrophils) are mediated through a transmembrane receptor that forms homo-oligomeric complexes upon ligand binding [3]. The common mode of action is to mobilise haematopoietic progenitor cells into the peripheral circulation. Fully differentiated neutrophilic granulocytes are functionally activated by G-CSF [4].

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In Europe, three different innovator rhG-CSF-containing biopharmaceuticals are approved with an independent marketing authorisation based on a full dossier. The active substances of these medicinal products are filgrastim, lenograstim and pegfilgrastim. G-CSF-containing biopharmaceuticals are primarily indicated to reduce the duration of neutropenia and the incidence of febrile neutropenia (FN) in cancer patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). The use of G-CSF-containing medicinal products to reduce the incidence of chemotherapy-induced FN in adult patients with lymphomas and solid tumours is now recommended in clinical practice guidelines from the first cycle when the overall risk of FN is  $\geq 20\%$  [5, 6]. Filgrastim or lenograstim is given daily until the patient's absolute neutrophil count (ANC) has recovered within the normal range. Pegfilgrastim is to be administered once per chemotherapy cycle.

## Filgrastim

Neupogen, the first therapeutic rhG-CSF product, was approved in 1991 [7]. The patent expired in Europe in 2006 and will expire in 2013 in the US. Filgrastim differs in structure from human G-CSF by having an additional amino-terminal methionine and no glycosylation (rmetHuG-CSF, 175 amino acids), but it shows the same *in vitro* and *in vivo* activity as endogenous G-CSF. Since marketing started, it is estimated that over 7.7 million patients have been exposed to Neupogen, and more than 26,000 have been treated in company-sponsored clinical trials [8]. According to the results of clinical trials, filgrastim is approved for adults to reduce the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation who are considered to be at increased risk of prolonged severe neutropenia, to mobilise peripheral blood progenitor cells (PBPCs), to increase neutrophil counts and reduce the incidence and duration of infection-related events in patients with severe congenital, cyclic or idiopathic neutropenia with ANC of  $\leq 0.5 \times 10^9/L$ , and to treat persistent neutropenia in patients with advanced HIV infection in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate. Filgrastim is also indicated for use in children in the cancer and severe chronic neutropenia settings. The originator filgrastim is approved for administration via IV infusion, continuous SC infusion or SC injection, depending on the indication to be treated and the individual circumstances. Filgrastim is rapidly absorbed after SC administration and exhibits first order kinetics. The elimination half-life is approximately 3.5 hours in healthy volunteers and cancer patients, independent of the method of administration. The primary route of elimination of filgrastim is glomerular filtration in the kidney.

## LENOGRASTIM

Granocyte was also launched in Europe in 1991 [9] and various other countries, but it is not approved in the US. The amino acid sequence of lenograstim is identical to endogenous G-CSF and filgrastim. Lenograstim, like the endogenous compound, is glycosylated in position 133. The carbohydrate moiety stabilises lenograstim. Bioavailability is dose dependent and decreases with increasing doses. The elimination half-life is 3–4 hours.

## Pegfilgrastim

Neulasta [10] is a second-generation biopharmaceutical, i.e. therapeutic properties of protein drugs are improved by modifying the molecular structure of the native proteins. Pegylation is one approach and has been used for several protein therapeutics by linking them to monomethoxy polyethylene glycol molecules of various chain lengths. In the case of filgrastim, the conjugation reduces the elimination by glomerular filtration. The elimination half-life is approximately 35 hours (26–46 hours interquartile range) in cancer patients [11]. One 6 mg dose of pegfilgrastim is recommended for each chemotherapy cycle to be administered by SC injection approximately 24 hours following chemotherapy. A single dose of pegfilgrastim increases the neutrophil count in a comparable or greater manner than filgrastim [12]. The peak serum concentrations occur one to five days after administration and serum concentrations are maintained during the period of neutropenia. At the onset of neutrophil recovery, the serum concentration of pegfilgrastim rapidly declines by neutrophil-mediated clearance—so-called self-regulating pharmacokinetics [13].

## MANUFACTURING PROCESS OF G-CSF-CONTAINING MEDICINAL PRODUCTS

Protein molecules, which have a far more complex structure than traditional small molecule drugs, are produced by living organisms. The use of living organisms introduces an inherent variability in the manufacturing process. To guarantee the quality and compliance of each production lot, detailed knowledge and control of the manufacturing process is required. Filgrastim is produced in *E. coli* K12. For the expression of the human gene in the bacteria, an additional N-terminal methionine is necessary. As bacteria are not capable of post-translational glycosylation, filgrastim is a pure protein molecule.

The manufacturing process of recombinant proteins in general consists of two phases: the first phase is the upstream processing (cell culture and fermentation, production of biomass), and the second phase is the downstream processing (isolation, purification of the active substance). Variations in the manufacturing processes may encompass different culturing and fermentation conditions, as well

as different purification methods and conditions (compare flow diagram, see Figure 1). Recombinant filgrastim is not excreted by the *E. coli* bacteria into the fermentation broth, but stored in inclusion bodies. Therefore the purification process starts with the isolation of the bacteria, followed by disruption, isolation and refolding of filgrastim. During the upstream and downstream processing, critical steps must be closely monitored by in-process controls.

Manufacturers of biosimilar products must develop proprietary expression systems and processing steps independently. Thus, biosimilars can never be identical copies of originator molecules, even when they have demonstrated comparable physicochemical and biological properties to a reference product using currently available tests [14].

## REGULATORY REQUIREMENTS FOR G-CSF-CONTAINING BIOSIMILARS

The main issue for the development of a biosimilar medicinal product in the EU is the demonstration of similarity in terms of quality, safety and efficacy to a reference product, which has to be the same throughout the development programme [15]. In favour of this principle, EMA has produced an overarching guideline on biosimilars [1] as well as guidance documents addressing quality issues [16], non-clinical and clinical issues [17], and guidelines setting out the requirements for specific biosimilars, including rhG-CSF [3]. The product class-specific guidance for rhG-CSF [3] is an annex to the general guidelines and was adopted by the Committee for Medicinal Products for Human Use in 2006. It is valid for filgrastim and lenograstim,

but not pegfilgrastim biosimilars (independent from the patent which lasts until 2015). The annex provides guidance for the demonstration of comparability of two rhG-CSF-containing medicinal products. The rhG-CSF biosimilars must undergo comprehensive comparability studies of both the drug substance and the drug product in order to provide evidence that the biosimilar is indeed similar in quality, safety and efficacy to a chosen filgrastim product that has the same pharmaceutical form, strength and route of administration and that is already approved in the EU. Sensitive test models must be used to detect potential differences. The reference product chosen is to be used throughout the whole comparability exercise. To date, only filgrastim biosimilars (reference product = Neupogen) have come to the market, see Table 1. The reason might be that lenograstim as glycosylated protein has to be produced in mammalian cells, which is more complex in manufacturing and quality control.

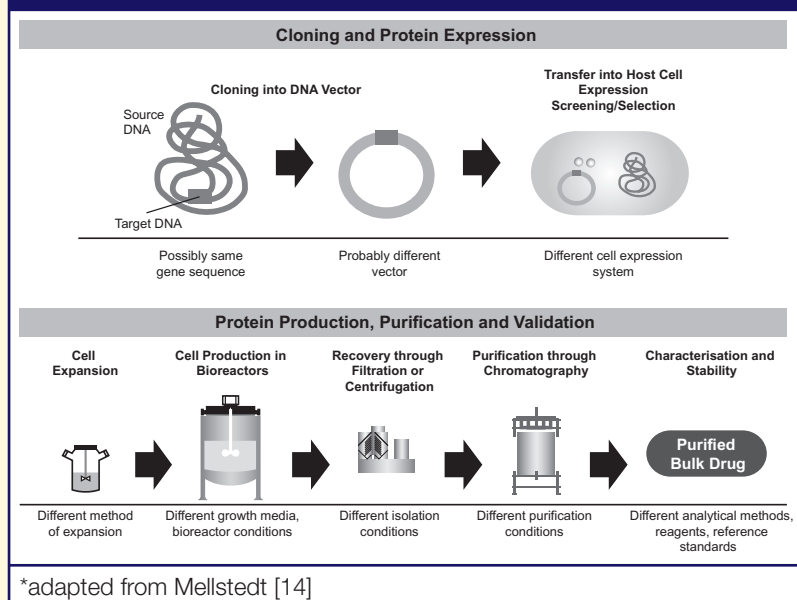
Manufacturers of biosimilar medicinal products have to present a full quality dossier, including detailed descriptions of their manufacturing processes, including validation, monitoring and other quality control procedures (chemistry, manufacturing, controls [CMC]). A CMC dossier of a biosimilar might have higher requirements than the CMC dossier of the reference product because of the additional comprehensive comparability exercise [15]. Applicants also have to perform non-clinical and clinical studies comparing the efficacy of the biosimilar product with the reference product. Phase II clinical studies are not necessary, while phase I and III studies should be performed. However, if similarity of the biosimilar product with the reference product has been convincingly demonstrated in a key indication, extrapolation to other indication(s) of the reference product may be possible without further clinical studies, if the mechanism of action is the same [1, 3]. The key indication is identified case-by-case for different biosimilar medicinal products in the guidelines. A biosimilar can have fewer, but not more, clinical indications than the reference product [15].

In conclusion, the required dossier for a biosimilar is reduced in comparison to a full dossier of an innovator product, but more intensive than a generic dossier where only identical physicochemical properties and bioequivalence in healthy volunteers needs to be shown.

## NON-CLINICAL STUDIES FOR RHG-CSF BIOSIMILARS

Biosimilar rhG-CSF-containing medicinal products are to be tested in non-clinical studies in comparison to the reference product, e.g.

Figure 1: Recombinant protein manufacturing and potential sources of variation in manufacturing processes\*



Amgen filgrastim (Neupogen). The studies should be designed to detect differences in pharmaco-toxicological response between the biosimilar and reference product. Pharmacodynamic studies are to be performed *in vitro* (cell based bioassays or receptor-binding assays) and *in vivo*. Neutropenic and non-neutropenic rodent models should be used to compare the pharmacodynamic effects of the products. With regard to toxicological studies, EMA requires at least one repeat dose toxicity study over at least 28 days. Special emphasis should be laid on the investigation of immune response to the products. EMA implemented a specific guideline for systematic immunogenicity assessment of biotechnology-derived therapeutic proteins [18] because unwanted immune response is a major concern in the use of therapeutic proteins. There are product-related and patient-related factors influencing the immunogenicity risk. With regard to the product-related factors, impurities such as host-cell proteins may play a role in recombinant products such as rhG-CSF. In this case, proteins arising from the manufacturing process induce a classic allergic reaction and provoke a T-cell-mediated immune response. With regard to patient-related factors, the immunogenicity risk is limited because the product is predominantly given to patients in combination with myelosuppressive chemotherapy and in the short term. The formation of aggregates and the breakdown of B-cell tolerance, especially in patients undergoing chronic administration, seems not to be a problem with rhG-CSF therapeutic use. Immune-related problems were not common in clinical trials or subsequent pharmacovigilance with the reference product [19-21].

## CLINICAL STUDIES

Only human *in vivo* studies can provide true comparative information for a proposed biosimilar. The

pharmacokinetic (PK) properties of the rhG-CSF biosimilar are to be compared in crossover studies using SC and IV administration. The pharmacodynamic (PD) effect is to be compared in healthy volunteers using the absolute neutrophil count (ANC) as a marker for the activity and the CD34+ cell count as secondary endpoint. The clinical study programme varied between the filgrastim biosimilars approved, see Table 2. For example, Hospira filgrastim was shown to have bioequivalent PK properties with Amgen filgrastim in a phase I, single-centre, open-label, randomised trial in 46 healthy volunteers [22, 23]. The comparability of the efficacy of Zarzio was accepted according to a comparative study in healthy volunteers [24]. The supportive trial in cancer patients was a non-comparative single-arm study [24]. XM02 was compared to Amgen filgrastim in a randomised, single-blind, single-dose crossover study in 196 healthy volunteers and also in cancer patients [25]. The PK profiles were comparable and there were no relevant differences with regard to duration of severe neutropenia and the incidence of FN in randomised controlled phase III studies in breast cancer, lung cancer and non-Hodgkin's lymphoma patients [25].

## CLINICAL EFFICACY STUDIES AND SAFETY

Applicants of biosimilar products have to present results of clinical studies, this requirement is a major difference to the approval procedure of generic drugs. Moreover, similarity to the reference product is to be demonstrated. Inferior, as well as superior, efficacy outside predefined limits would contradict the assumption of similarity. The recommended clinical model for the comparability exercise of the rhG-CSF biosimilar and reference product is the prophylaxis of severe neutropenia after cytotoxic chemotherapy in a homogenous patient group [3]. If frequency and duration of neutropenia is known in the selected chemotherapy

**Table 1: Overview of rhG-CSF filgrastim products licensed in Europe (innovator and biosimilars)**

	Invented name	Marketing authorisation holder	Date of authorisation	Manufacturer responsible for batch release
Innovator	Neupogen	Amgen Europe BV	1991	Amgen Europe BV
Biosimilars to filgrastim	Ratiograstim Filgrastim ratiopharm	ratiopharm GmbH	Sept 2008	Merckle Biotec Ulm, Germany
	Tevagrastim	Teva Generics GmbH	Sept 2008	Teva Pharma, The Netherlands
	Biograstim	CT Arzneimittel GmbH	Sept 2008	Merckle Biotec Ulm, Germany
	Filgrastim Hexal	Hexal AG	Feb 2009	Sandoz GmbH, Austria
	Zarzio	Sandoz GmbH	Feb 2009	
	Nivestim	Hospira UK Ltd	June 2010	Pliva Krakow, Poland

regimen, a two-arm comparability study is sufficient. If other chemotherapy regimens are used, a three-arm study including placebo may be needed. The primary endpoint is duration of severe neutropenia (ANC,  $500 \times 10^3/\text{mL}$ ). The equivalence margin is predefined as  $\pm 1$  day for the difference in duration of severe neutropenia. The incidence of FN, infections and the cumulative rhG-CSF dose are secondary endpoints. In the published summary of the European regulatory assessment (European Public Assessment Reports [EPARs]) of the rhG-CSF biosimilars, EMA states that clinically non-relevant differences with regard to the duration of severe neutropenia were observed in comparison to the reference products [22, 24, 25]. All of the approved indications, except chemotherapy-induced neutropenia of filgrastim biosimilars, see Table 2, are extrapolated. Although not tested in children the benefits are expected to be the same. In the summary of product characteristics (SPC) it is not obvious which indications were tested and which are extrapolated [26-28]. References indicating the biosimilar nature of the product and data from the biosimilar clinical studies (PK, PD and safety sections) have been more frequently included in the SPC, but further clarity is still needed in some cases.

The development programmes of the rhG-CSF biosimilars were not associated with unexpected safety issues. Although immunogenicity problems have been rare with Amgen filgrastim, EMA provides guidance that safety data should be collected after repeated dosing, preferably in a comparative clinical trial over treatment courses with several cycles [3]. Patients should be followed up for at least six months. During the clinical studies with Nivestim two patients gave a positive antibody response and three patients in the Nivestim treatment group had one or more post-treatment samples with a borderline positive result.

There was no evidence of a clinical effect on efficacy (neutrophil counts) or safety in the patients with borderline positive results. No patient in the Neupogen treatment group was tested positive for G-CSF antibodies [28]. When the formation of antibodies against XM02 and Neupogen was investigated in the three cancer patient studies the incidence of binding and neutralising antibodies was low [25]. According to the EPARs of filgrastim biosimilars, additional long-term safety and immunogenicity data will be collected post-marketing as defined in the risk management plans, see Table 3.

### CHARACTERISTICS OF EMA APPROVED FILGRASTIM BIOSIMILARS

The currently available filgrastim products in Europe—innovator and biosimilars—are listed in Table 1. The active substance of Neupogen is produced by Amgen US, and Amgen Europe is responsible for batch release. The company has extensive knowledge and first-hand expertise in the manufacturing of biopharmaceuticals. There are already seven filgrastim biosimilars approved by EMA. The seven marketing authorisations refer to three different products. Filgrastim XM02 received four marketing authorisations as Filgrastim ratiopharm, Ratiograstim, Tevagrastim and Biograstim. Filgrastim EP2006 received two marketing authorisations as Hexal and Zarzio. The items of these two groups of products could be referred to as bioidentical as they are derived from the same expression system, using the same manufacturing process and formulation, and they are approved by the same dossier. The active substances are produced by the same manufacturer, but different manufacturers are responsible for batch release of the finished product and the brand names are different. The third filgrastim product, Nivestim, is manufactured and marketed by Hospira.

Table 1: (Continued)

Manufacturer of the biological active substance	Dosage forms	Excipients	Storage	Maximum shelf life
Amgen Inc	30 MU 48 MU prefilled syringes (0.5 mL) vials (1 mL, 1.6 mL)	sodium acetate, sorbitol, polysorbate 80, water for injections	2°C–8°C	30 months
Sicor Biotech Vilnius, Lithuania	30 MU 48 MU prefilled syringes	acetic acid, glacial sodium hydroxide, sorbitol, polysorbate 80, water for injections	2°C–8°C no further information	30 months
Sandoz GmbH, Austria	30 MU 48 MU prefilled syringes	glutamic acid, sorbitol, polysorbate 80, water for injections	2°C–8°C light protected	30 months
Hospira Zagreb Croatia	12 MU 30 MU 48 MU prefilled syringes	acetic acid, glacial sodium hydroxide, sorbitol, polysorbate 80, water for injections	2°C–8°C maximum 48 hours outside refrigerator	24 months

rhG-CSF: recombinant human granulocyte colony-stimulating factor.

**Table 2: Information presented at registration for biosimilar rhG-CSF products (pivotal patient studies)**

Approved indications	Neupogen [7, 40]	Ratiograstim [36], Filgrastim ratiopharm [37], Biograstim [38], Tevagrastim [25]	Filgrastim Hexal [39] Zarzio [24]	Nivestim [22]
Chemotherapy-induced neutropenia	Phase III RCTs in patients with SCLC and <i>de novo</i> AML Supportive data from patients with urothelial and ovarian cancer, SCLC, BC, neuroblastoma and various non-myeloid malignancies	Phase III RCT in patients with BC, comparative cross-over design Supportive phase II/III safety studies in patients with lung cancer and NHL	Supportive <sup>†</sup> phase III, single arm, non-comparative study in patients with BC <sup>†</sup> Approval granted based on PD study in healthy volunteers	Phase III RCT in patients with BC, comparative non-cross-over design
Myeloablative therapy/BMT	RCTs in patients with HD and NHL, or various myeloid and non-myeloid malignancies treated with myeloablative therapy and autologous or allogeneic BMT Supportive data from patients with BC, malignant melanoma, HD, NHL, ALL and germ cell tumour who received autologous BMT	*	*	*
PBPC mobilisation	Mobilisation studies in heavily pre-treated patients with NHL, HD or ALL, pre-treated BC patients and other patients with prior exposure to chemotherapy and chemotherapy-naïve patients Engraftment assessed following transplant of Neupogen-mobilised PBPC	*	*	*
Chronic neutropenia	Phase III of children and adults with SCN	*	*	*
HIV persistent neutropenia	Multicentre RCT of patients with HIV infection Supportive data from three open-label, non-randomised studies in patients with HIV infection	*	*	*

AML: acute myeloid leukaemia; ALL: acute lymphoblastic leukaemia; BC: breast cancer; BMT: bone marrow transplant; CIN: chemotherapy-induced neutropenia; HD: Hodgkin disease; HIV: human immunodeficiency virus; NHL: non-Hodgkin lymphoma; PBPC: peripheral blood progenitor cell; PD pharmacodynamic; RCT: randomised controlled trial; rhG-CSF: recombinant human granulocyte colony-stimulating factor; SCLC: small cell lung cancer; SCN: severe chronic neutropenia.  
\*Extrapolated, approved indication.

All filgrastim biosimilars carry the same international non-proprietary name (INN) for the active substance, i.e. filgrastim. The INN is allocated by a committee of the WHO according to the manufacturer's application. In the case of erythropoietin biosimilars, identical and different INNs were allocated which can be confusing for the prescribers. In the case of filgrastim biosimilars, all products carry the same INN, which makes the prescribing and distribution difficult and may lead to automatic substitution. From a pharmacist's perspective, biosimilar products should be labelled as such and biosimilar character should become obvious from the INN name. The differentiation is especially relevant with regard to pharmacovigilance and traceability. Until the INN naming system for biosimilars is improved, the brand name should be used in addition to the INN in prescribing and documentation.

Extrapolation to indications of the filgrastim innovator drug, which were not studied in clinical trials, is permitted as stated in the corresponding guideline and the favourable risk-benefit balance described in the EPARs. In the absence of efficacy and safety data for stem cell mobilisation in healthy donors, the European Group for Bone and Marrow Transplantation does not recommend the use of G-CSF biosimilars in this indication [29]. A number of patients should be treated with G-CSF biosimilars before they are given to healthy donors. This uncertainty is acknowledged by EMA in the EPAR of XM02: in the risk-benefit assessment of extrapolated indications, the mobilisation of peripheral blood progenitor cells as an extrapolated indication is questioned because an identical mechanism of action is not proven explicitly [25]. This issue is addressed in the risk management plans of the biosimilar products,

**Table 3: Risk management plan presented at registration for each biosimilar rhG-CSF product according to the European public assessment reports**

Safety concern (subset)	Ratiograstim, Filgrastim ratiopharm, Biograstim, Tevagrastim [25]	Filgrastim Hexal Zarzio [26]	Nivestim [22]
Severe splenomegaly Severe pulmonary distress syndrome/adult respiratory distress syndrome (ARDS) Cutaneous vasculitis Exacerbation of rheumatoid arthritis Allergic reactions Osteoporosis Transformation to leukaemia or MDS in patients with SCN		Pharmacovigilance plan in patients with SCN Phase IV study (12-month treatment) Safety follow-up of study patients in cooperation with SCN European registry, 5 years in total Cooperation with apheresis centres for healthy stem cell donors	Targeted follow-up Follow up of the patients through SCN registry
Malignant cell growth in patients with SCN Sweet's syndrome Alveolar haemorrhage Severe sickle cell crisis			Targeted follow-up Follow up of the patients through SCN registry
Immunogenicity	Signal procedure for all incoming ADR reports from whatever sources Cooperation with SCN registry and analysis of corresponding data	Pharmacovigilance plan in patients with severe chronic neutropenia Phase IV study (12-month treatment)	Targeted questionnaire
Haematological malignancy in normal donors	Signal procedure for all incoming ADR reports from whatever sources Literature search for publications on haematological malignancies related to rhG-CSF use	Cooperation with apheresis centres for healthy stem cell donors, 5 years after mobilisation. Safety follow-up of healthy subjects of phase I study EPO6-103	Targeted questionnaire Cooperative programme with haematological transplant centres
Increased risk of GVHD Interaction with myelosuppressive cytotoxic chemotherapy Interaction with lithium Off-label use			Targeted questionnaire
Long-term use			Specialised follow-up for long-term data

ADR: adverse drug reaction; GVHD: graft-versus-host disease.

see Table 3. Careful monitoring is necessary because of side effects such as immunogenicity, normal white blood cell function and leukaemogenesis [14].

### GOOD HANDLING PRACTICE

The rhG-CSF-containing medicinal products are to be administered parenterally. Vials, syringes or pen presentations are authorised—the range of presentations is summarised in Table 2. To administer standard doses, ready-to-use syringes are advantageous—they are easier to transport and to handle and allow more accurate and reproducible dosing than vials, thereby improving safety and treatment adherence for patients. In order to prepare individually calculated doses for paediatric patients, solutions in vials are more appropriate. Nivestim is

marketed in a 12 MU dose prefilled syringe, which may be useful in a limited weight range, but is not as appropriate as a vial for preparing paediatric dosages.

The filgrastim-containing medicinal products are, without exception, marketed in liquid form and should be stored in the refrigerator at 2°C–8°C. Recommended storage time outside the refrigerator is claimed differently for the different products, see Table 1. Accidental exposure to freezing temperatures does not adversely affect the stability [7]. All products are approved for SC and IV administration. For infusion, the approved products may be diluted with 5% glucose solution, but are incompatible with 0.9% sodium chloride solution, which causes precipitation of filgrastim. The integrity of filgrastim in diluted solutions depends on

the filgrastim concentration. Dilution to a final concentration less than 0.2 MU (2 µg) per mL is not recommended at any time. When filgrastim is diluted to concentrations below 1.5 MU (15 µg) per mL, human serum albumin (HSA) should be added to a final concentration of 2 mg/mL in order to avoid significant adsorption to plastic materials. Diluted filgrastim solutions prepared in this way are compatible with glass bottles, polyolefin and PVC bags, and polypropylene syringes. Prefilled syringes and vials are free from preservatives and are for single use only.

## PHARMACOVIGILANCE PLAN, POST-MARKETING SAFETY

In general, the acute safety profiles of biosimilar and innovator products are similar, but the number of patients in biosimilar clinical trials is smaller and the observation period is short. Pharmacovigilance programmes are therefore extremely important. Within the application procedure for a biopharmaceutical or biosimilar, the applicant should present a risk management programme/pharmacovigilance plan. Selected safety concerns and risk management procedures proposed in the applicants' risk management plans are shown for filgrastim biosimilars in Table 3. Screening for rare immunological adverse effects in the post-marketing setting is difficult; it is necessary to remind physicians and pharmacists at regular intervals. The repeated switching of products also makes it difficult to accomplish the pharmacovigilance programme, see also interchangeability.

## INTERCHANGEABILITY

Biosimilars should not be interchangeable with originator molecules, or with each other, unlike traditional small-molecule generic drugs. In fact, the EMA has stressed that because biosimilars and their reference molecules are not identical, the decision to treat a patient with a reference or biosimilar should be based on the opinion of a qualified healthcare professional [30]. Automatic substitution is prohibited by law in some European countries [31], in other countries there are guidelines against automatic substitution of biosimilars [32]. The main concern with automatic substitution is the lack of traceability of which product caused the reported side effects when products are mixed. Because of the different activities laid down in the risk management plans of the different filgrastim biosimilars, an automatic interchange would render it difficult or impossible to accomplish the defined risk management activities. In the case of filgrastim biosimilars, the automatic interchange is especially to be avoided in healthy donors.

## EVALUATION OF FILGRASTIM BIOSIMILARS BY PHARMACISTS

When considering use of biosimilar filgrastim, healthcare professionals will need to consider clinical efficacy, safety and tolerability issues [33], see Table 4. Clinicians

**Table 4: A checklist of issues to consider in selecting a rhG-CSF biosimilar product**

Manufacturer
<ul style="list-style-type: none"> <li>• Reputation, reliability, experience with biopharmaceuticals</li> <li>• Location of manufacture of the medicinal product</li> <li>• Location of the manufacture of the active drug substance (are third parties involved?)</li> <li>• Information about safety updates</li> </ul>
Protein quality and formulation
<ul style="list-style-type: none"> <li>• Formulation: choice of excipients, stabilisers and preservatives</li> <li>• Dosage form and administration device, teaching materials for use of a different safeguard prefilled syringes</li> <li>• Shelf life, susceptibility to degradation when not refrigerated</li> <li>• Consistency between batches, appropriate quality controls</li> </ul>
Reliability of supply
<ul style="list-style-type: none"> <li>• Stock position</li> </ul>
Clinical efficacy
<ul style="list-style-type: none"> <li>• Clinical trials carried out with different batches of the biosimilar product itself: adequacy of design, results, consistency and reliability of extrapolation of results</li> </ul>
Clinical safety and tolerability
<ul style="list-style-type: none"> <li>• Comparison of safety and tolerability profile with reference product</li> <li>• Immunogenicity (especially as compared to reference product)</li> <li>• Precautions or contraindications for use of the biosimilar</li> <li>• Feasibility and effort for post-marketing risk management programmes</li> </ul>
rhG-CSF: recombinant human granulocyte colony-stimulating factor.

and pharmacists should inquire where the product is manufactured, whether the active drug substance is manufactured by the holder of the marketing authorisation or by a third party, and how information is disseminated to the healthcare community about changes in the manufacturing process and about safety updates. Although rhG-CSF innovator products and biosimilars are usually not administered over a long time like erythropoietin or insulin, reliability of supply is essential. This is particularly true in the hospital market, where reliability of supply is of the utmost importance in order to achieve efficient buying and stock management. It is also necessary to have a sustainable supply chain that can deliver products on time and under guaranteed conditions, such as a safe cold chain.

Any differences between the biosimilar and the originator molecule with regard to formulation (including the choice of excipients, stabilisers and preservatives), or dosage form and administration device, should be made explicit to

the healthcare providers. The known safety and tolerability profile of the biosimilar, as well as precautions or contraindications for its use, should be compared with those of the originator molecule. In the case of filgrastim biosimilars, differences in the indications tested and number of patients included in clinical trials should be noted. Given that clinical trials which enrol relatively small numbers of patients cannot identify rare side effects, it is obligatory to monitor safety closely during the post-approval phase. Although the development of antibodies to filgrastim occurs infrequently and no clinical consequences with regard to efficacy and tolerability have been described, EMA asks for attention to be paid to immunogenicity. Finally, clinicians should be familiar with the post-marketing risk management programme in place for the biosimilar product. As patients should always be monitored closely when switched from the originator product to a biosimilar or from one biosimilar to another one [34], each switch means an additional effort.

## CURRENT MARKET SITUATION (PRICING AND VALUE)

Price, tax rates and reimbursement policies for medicinal products are different across Europe. Some countries adopt biosimilars more quickly than others, which seems to be related to the national healthcare system and also the type of product. Some biosimilar products are rated as more critical than others, e.g. erythropoietin, because of the high immunogenicity risk. To my knowledge, to date, pharmacoeconomic studies comparing the filgrastim originator product with filgrastim biosimilars have not been published. For pegfilgrastim, a health economic model to assess overall costs was published [35]. To make sound decisions it would be useful to know the treatment costs with the biosimilar in comparison to the reference product and results of cost-efficacy studies. Because clinical trials are required for the approval procedure of biosimilars and costs of production are higher in comparison to small

molecules, discounts for biosimilars amount to approximately 30% (published list prices), in comparison to > 70% for generics. Hospital pharmacists are interested in obtaining more insight into the price calculation.

## SUMMARY AND CONCLUSION

Biosimilars are by definition not identical to their corresponding originator biopharmaceuticals, and should therefore not be considered interchangeable in the same way that traditional small molecule generic drugs are interchangeable with the original products. Any apparently minor modification in the manufacturing or formulation of a product such as filgrastim, or in the administration device, has the potential to cause untoward clinical consequences, even if the product appears to be physicochemically equivalent to an accepted reference standard. For this reason, EMA has developed robust regulatory requirements before marketing authorisation can be granted for a biosimilar. Clinicians and pharmacists should consider several critical issues regarding the manufacture, protein quality and formulation, supply and clinical efficacy, safety and tolerability, and substitution of products in order to make informed decisions about the use of biosimilar filgrastim.

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## CONFLICT OF INTEREST

I have been a consultant, speaker and member of advisory boards of various (bio)pharmaceutical companies, which had no influence on the content of this article.

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