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The regulatory framework of biosimilars in the European Union

Paola Minghetti[1], Paolo Rocco[1], Francesco Cilurzo[1], Lucia Del Vecchio[2] and Francesco Locatelli[2]

[1] Department of Pharmaceutical Sciences "P. Pratesi", Università degli Studi di Milano, via G. Colombo, 71–20133 Milan, Italy
[2] Department of Nephrology, Dialysis and Renal Transplant, A. Manzoni Hospital, Via dell'Eremo 9, 23900 Lecco, Italy

In the European Union (EU), the regulatory policy for biosimilars has enabled different biosimilar products to be marketed through an abridged application, which allows the applicant to submit a reduced dossier. Nevertheless, some manufacturers of biological products that share some characteristics with copies have opted for a full application; therefore, the number and extent of clinical studies required in these cases is increased. Here, we focus on a comparison of recombinant human erythropoietin medicinal products. We analyse and discuss clinical studies submitted to the European Medicines Agency that relate to available biosimilars and biological medicinal products that are authorised with a full dossier. We also discuss the issues of interchangeability and substitution, given that the EU allows each Member State to set their own substitution policies.

Introduction

The patent expiration of some major biotechnology-derived medicines, namely monoclonal antibodies and therapeutic proteins, has led to the manufacture of copies of the innovator's products. After the data protection has expired, the Marketing Authorisation Application (MAA) for a copy can be handled as an abridged application, where some of the data are available and a reduced dossier can be accepted. Thus, the possibility arises for more copies to hit the market, boosting competition in the pharmaceutical industry.

A copy that has been granted a Marketing Authorisation (MA) within the European Union (EU) is defined as a 'similar biological medicinal product' or 'biosimilar', and its MA is accompanied by a reduced dossier (discussed below). Unlike generics, which contain the same (small molecule) active substance(s) as that of a reference medicinal product and have a bioequivalence demonstrated through appropriate bioavailability studies, biosimilars are demonstrated to be similar but not identical to their reference products. Their chemical characteristics are directly related to the manufacturing process, and cannot be precisely duplicated, owing to their complex structure and to the strong relationship between the manufacturing processes and the characteristics of the final product [1]. Moreover, because analytical techniques are not always able to detect or predict all biological and clinical properties of proteins, differences between biopharmaceutical products can remain undetected and, even when detected, subtle differences are difficult to interpret [2]. Thus, to grant a MA for biosimilars, a different approach is required compared with that used for originators and generics [3].

In Europe, the legal basis for biosimilars was established by an EU Directive,[1] which lays down the requirements for the MAAs based on the demonstration of the similar nature of two biological medicinal products, with the requirement that the amount of nonclinical and clinical data are determined on a case-by-case basis in accordance with relevant scientific guidelines. Regulation EC No. 726/2004, which was issued by the European Parliament in 2004, lays down Community procedures for the authorisation and supervision of medicinal products that need a centralised procedure, including biotechnological medicinal products. At the same

Corresponding author:. Minghetti, P. (paola.minghetti@unimi.it)

[1] Article 10(4) and Section 4, Part II, Annex I to Directive 2001/83/EC, as amended by Directive 2007/27/EC.

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time, the regulatory policy for biosimilars is governed mainly by the European Medicines Agency (EMA), through both general guidelines addressing quality, nonclinical and clinical issues, and additional product class-specific guidelines.

Here, we analyse the market in terms of available biosimilar medicines and the clinical studies submitted to the EMA for approval of recombinant human erythropoietin. The comprehension of the regulatory approach can be useful to improve the knowledge on the marketed drugs, their differences and similituds.

The legislative framework

MAA of biosimilars

In the EU, technologically advanced medicinal products, such as those developed by means of a biotechnological process (e.g. recombinant DNA technology), can be placed on the market only after a MA has been issued by the Community in accordance with the provisions of Regulation (EC) No. 726/2004[2] (centralised procedure). The same regulation also provides an alternative procedure, where clinical data can be omitted in the case of exceptional circumstances. In addition, a centralised procedure can lead to a conditional MA under the provisions of Regulation (EC) no. 507/2006.

The application must be accompanied by a dossier containing the required data, presented in a standardised format, namely the Common Technical Document (CTD). The CTD comprises five modules: module 1 provides specific administrative data; module 2 provides quality, nonclinical and clinical summaries; module 3 provides chemical, pharmaceutical and biological information (i.e. quality); module 4 provides nonclinical reports (i.e. safety); and module 5 provides clinical study reports (i.e. efficacy).[3] Several CTD variations, such as production method or product specification, can be submitted by the MA holder to the competent authority and the application can then be implemented generally after a positive evaluation.

When patent rights, supplementary protection certificates and the relevant period of data protection, established over a 10-year period[4] (or 11 years if 'an application is made for a new indication for a well-established substance, provided that significant preclinical or clinical studies were carried out in relation to the new indication'[5]) expire, it seems unethical and uneconomical to ask other applicants to provide a full dossier for a copy of that particular medicinal product. Thus, the extent of data to be submitted varies. In the case of a copy of a small-molecule chemical entity, the applicant is not required to provide the results of preclinical tests and clinical trials if it is possible to demonstrate, through appropriate bioavailability studies, that the copy (generic) is bioequivalent to the originator.

In the case of the copy of a biological medicinal product, because the active substance is similar but not identical to those in the innovator product, the requirements for MAAs are based on the demonstration of the similar nature of the two biological products through comparability studies, named the 'comparability exercise'. The comparability exercise is needed to generate evidence substantiating the similar nature in terms of quality, safety and efficacy of the new similar biological medicinal product and the chosen reference medicinal product authorised in the EU [4].

The comparability exercise

The number and extent of comparability studies required for granting a MA are detailed in guidelines issued by the EMA's Committee for Medicinal Products for Human Use (CHMP). These guidelines cover a range of issues, including manufacturing, demonstration of comparability for quality (module 3), nonclinical (module 4) and clinical study (module 5) reports, physicochemical and biological analyses and clinical trial requirements, and additional data (i.e. toxicological, other nonclinical and appropriate clinical data) whose relevance has to be determined on a case-by-case basis, owing to the complexity and diversity of the products. The purpose of the comparability exercise is to demonstrate the similar nature of the biosimilar and the reference product and, consequently, to reduce the amount of data to be submitted in modules 4 and 5 of the CTD.

The comparability exercise has been introduced by the US Food and Drug Administration (FDA) to allow manufacturers of 'well-characterised biopharmaceutical products' (i.e. proteins whose identity, purity, impurities, potency and quantity can be determined and controlled) to implement changes in the manufacturing process. This includes a change in manufacturing site, or modification to cell and seed strains, or fermentation and purification processes, in most cases without conducting additional clinical trials to demonstrate efficacy [5].

In 2000 [6] and 2002 [7], the EMA issued two guidelines on comparability of medicinal products containing biotechnology-derived proteins as the active substance, relating to quality, and nonclinical and clinical issues, respectively. Even if not stated in the title, the two guidelines clearly addressed the issue of a change in the manufacturing process. The EMA then broadened the scope of comparability to biological medicines produced by different manufacturers, by publishing the overarching guideline on similar biological medicinal products in 2004 [4] and two guidelines covering quality [8] and nonclinical and clinical [9] issues of biosimilars were published in 2005 (EMA; http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000086.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002754a]. The 2000 and 2002 guidelines were updated in 2003 [10] and 2006 [11], respectively to refer explicitly to changes in the manufacturing process only.

Additional product class-specific guidelines on preclinical and clinical studies have been developed for several therapeutic proteins, providing guidance on appropriate pharmacodynamic and toxicological studies (in the nonclinical section), and on pharmacodynamic, pharmacokinetic, efficacy and safety studies (in the

[2] Regulation (EC) No, 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, as amended.

[3] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended.

[4] Article 10, paragraph 1, Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended.

[5] Article 10, paragraph 5, Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended.

clinical section). In the case of biosimilars containing recombinant human erythropoietins, the EMA guideline has been recently revised [12], drawing on experience gained from the products authorised over the past few years.

It is clear that the dossier for a biosimilar is more cumbersome than that of a generic medicinal product. They both comprise full modules 1, 2 and 3, but biosimilars need the comparability exercise for modules 3, 4 and 5, whereas in the case of generics, module 4 is omitted and module 5 is replaced by demonstration of bioequivalence [13].

Manufacturing and marketing

Biosimilar medicines in the EU

For every biosimilar product on the market, it is possible to identify: (i) the manufacturer of the biological active substance; (ii) the manufacturer responsible for batch release; and (iii) the MA holder.

Owing to the complexity of development and the manufacturing of biotechnologically active substances, the practice of co-marketing is more bulky than in other fields of the pharmaceutical industry. Indeed, in many cases, for products marketed with different brand names, either the first or the first two manufacturers from the above list are linked to the same company. The 14 biosimilar medicinal products currently marketed in the EU are listed in Table 1 and analysed below.

Somatropin. Omnitrope®, the first biosimilar in Europe, hit the market in 2006. It is manufactured and marketed by Sandoz, a Novartis Company (Novartis was created in 1996 through the merger of Ciba-Geigy and Sandoz). Valtropin is manufactured by LG Life Sciences and marketed by its partner, Biopartners.

Epoetin. Three epoetin products with the same International Nonproprietary Name (INN) (recombinant human erythropoietin alfa) are manufactured by Rentschler Biotechnologie (owned by Dr Rentschler Holding, who sold their subsidiary, Rentschler Arzneimittel, to Medice). The products are marketed by Sandoz, as Binocrit, and by its licensees Medice, as Abseamed, and by Hexal, as Epoetin alfa Hexal.

Two epoetin zeta products are manufactured by Norbitec, a joint venture between Stada, Bioceutical and Normark, and co-marketed by Stada and Hospira. Stada markets its products through a net of sales companies, which bear different names across Europe, such as Hemofarm (Bosnia-Herzegovina and Romania); Aliud Pharma (Czech Republic); PharmaCoDane (Denmark); EG (France); EG and Crinos, which is primarily responsible for branded products (Italy); Clonmel Healthcare (Ireland); Hemomont (Montenegro); Centrafarm (the Netherlands); Ciclum Farma (Portugal); Nizhpharm (Ukraine); and Genus Pharmaceuticals (UK).

Not all epoetin-based products manufactured after the first originators are biosimilars. For example, Neorecormon is an epoetin beta that was authorised in 1997 and is manufactured and marketed by Roche. Biopoin and Eporatio are epoetin thetas, and were authorised in 2009. They are manufactured by Merckle Biotec and marketed by CT Arzneimittel and Ratiopharm, respectively. For these products, a full dossier was provided. Below, we compare the clinical studies performed in the case of epoetin theta and an epoetin biosimilar.

Filgrastim. Four filgrastim products are manufactured by Sicor Biotech, a subsidiary of Teva Group. Two of them are marketed by two other subsidiaries of Teva: Ratiopharm and CT Arzneimittel. Merckle Biotec, the subsidiary of Ratiopharm that produces active biopharmaceutical substances, is the manufacturer responsible for batch release of three products.

Nivestim is manufactured by Hospira in the biopharmaceutical facility in Croatia, acquired in 2009 (along with Nivestim rights)

TABLE 1

Biosimilar products marketed in the EU[a]

Medicinal product	INN	Reference medicinal product	MA holder	Manufacturer responsible for batch release	Manufacturer of active substance	MA date
Omnitrope	Somatropin	Genotropin	Sandoz	Sandoz	Sandoz	4/2006
Valtropin	Somatropin	Humatrope	BioPartners	BioPartners	LG Life Sciences	4/2006
Retacrit	Epoetin zeta	Eprex/Erypo	Hospira	Stada	Norbitec	12/2007
Silapo	Epoetin zeta	Eprex/Erypo	Stada	Stada	Norbitec	12/2007
Abseamed	Recombinant human erythropoietin alfa	Eprex/Erypo	Medice	Hexal	Rentschler Biotecnologie	8/2007
Binocrit	Recombinant human erythropoietin alfa	Eprex/Erypo	Sandoz	Hexal	Rentschler Biotecnologie	8/2007
Epoetin alfa Hexal	Recombinant human erythropoietin alfa	Eprex/Erypo	Hexal	Hexal	Rentschler Biotecnologie	8/2007
Biograstim	Filgrastim	Neupogen	CT Arzneimittel	Merckle Biotec	Sicor Biotech	9/2008
Filgrastim Ratiopharm	Filgrastim	Neupogen	Ratiopharm	Merckle Biotec	Sicor Biotech	9/2008
Ratiograstim	Filgrastim	Neupogen	Ratiopharm	Merckle Biotec	Sicor Biotech	9/2008
Tevagrastim	Filgrastim	Neupogen	Teva Generics	Teva Pharma	Sicor Biotech	9/2008
Nivestim	Filgrastim	Neupogen.	Hospira	PLIVA Kraków	Hospira Zagreb	6/2010
Zarzio	Filgrastim	Neupogen	Sandoz	Sandoz	Sandoz	2/2009
Filgrastim Hexal	Filgrastim	Neupogen	Hexal	Sandoz	Sandoz	2/2009

[a] In addition to the MA holder, the manufacturers of the biological active substance and finished product are listed to highlight the cases of co-marketing.

from Pliva, a former partner of Hospira in the manufacturing of filgrastim and now owned by Teva group. The two other products are manufactured by Sandoz and manufactured either by Sandoz or Hexal.

Clinical studies on biosimilar and originator products: epoetin

Here, we compare clinical studies for biosimilar products containing epoetin (HX575, SB309) and the most recent originators (Epoetin theta as Biopoin and/or Eporatio). The case of epoetin is particularly relevant because the regulatory requirements are more stringent than for other recombinant proteins, reflecting its clinical history, especially the cases of pure red cell aplasia (PRCA) reported in 2002 [2]. In particular, similar clinical efficacy should be demonstrated in at least two randomised, preferably double-blind, parallel group clinical trials, as opposed to one two-arm study, as done for somatropin and filgrastim biosimilar products. Data must be provided for both intravenous (i.v.) and subcutaneous (s.c.) routes of administration (separate clinical trials for both routes or one clinical trial for one route plus adequate bridging data for the other route [12,14]).

HX575

HX575 (Abseamed®, Binocrit®, Epoetin alfa Hexal) has undergone five pharmacokinetic/pharmacodynamic studies in healthy volunteers using single-dose and multiple-dose administration schedules given i.v. or s.c. (Table 2). These studies showed similar pharmacokinetics profiles of HX575 given i.v. and s.c. and Eprex®/Erypo® under steady-state conditions. The pharmacodynamic effects of HX575 were examined as part of the pharmacokinetic studies as suggested in the guidance on similar biological medicinal products containing recombinant erythropoietins. The same i.v. or s.c, dose of HX575 and Eprex/Erypo caused similar increases in haemoglobin (Hb) levels in healthy volunteers.

One double-blind, randomised, parallel-group, multicentre study (INJ-9) [15] was performed comparing HX575 given i.v. ($n = 314$) with Eprex/Erypo ($n = 164$) in patients undergoing haemodialysis with anaemia secondary to chronic kidney disease (CKD). In both the intention-to-treat (ITT) and per-protocol (PP) population, the confidence interval (CI) of the mean change in Hb in the HX575 and Erypo group both remained within the predefined range of ±0.5 g/dl levels. The percentage of patients with Hb levels within the target or having dose changes during the study was also similar in the two groups. The mean weekly epoetin dose decreased in both treatment groups from baseline to the evaluation period, but this was more evident for Erypo than for HX575 [−739 IU/week (8.9%) and −314 IU/week (2.2%), respectively]. However, this was not considered enough for not supporting therapeutic equivalence between Eprex/Erypo and HX575 (the safety data were comparable). At the time of the MAA of HX575, epoetin alfa was not administered s.c. in patients with CKD because of the risk of PRCA; therefore, a comparative study using this administration route in patients with CKD was not feasible. Such a study was performed some years later following MA, but it was halted after the occurrence of one PRCA case and one positivity for antierythropoietin antibodies [16].

The company also presented the results of a noncomparative, controlled study (INJ-11) in 114 patients with cancer who were receiving chemotherapy (40 patients were allocated to treatment with Eprex/Erypo as a measure of internal validity) [12]. Treatment response, defined as an increase in Hb concentration ≥2.0 g/dl from baseline, was higher in the HX575 than in the Eprex/Erypo group, but the study design did not allow reliable comparisons. Given the small sample size, therapeutic equivalence between HX 575 and Erypo for the s.c. route of administration could not be concluded but was considered as being probable. Following these studies, the therapeutic indications of HX575 are superimposable to those of Eprex.

SB309

The pharmacokinetic properties of SB309 (Retacrit®, Silapo®) and the reference product Erypo were compared in two pharmacokinetic studies in healthy volunteers after single dose s.c. and i.v. administration (Table 3). Primary analysis suggested subavailability of SB309 compared with Erypo; however, this was not confirmed after correcting epoetin serum concentrations for the total protein content of single batches. No specific pharmacodynamic studies were conducted with SB309. Indeed, the pharmacodynamics of erythropoietin is known and is described in the

TABLE 2

Pharmacokinetic/pharmacodynamic and clinical studies for biosimilar product HX 575 (recombinant human erythropoietin alfa), marketed as Abseamed, Binocrit or Epoetin Alfa Hexal

Study identification code	Subject number (enrolled)	Reference medicinal product	Route	Primary end point
INJ-4 (Phase I)	6	Eprex/Erypo	s.c./i.v.	–
INJ-5 (Phase I)	76	Eprex/Erypo	i.v.	–
INJ-6 (Phase I)	72	NeoRecormon	s.c	–
INJ-7 (Phase I)	6	–	s.c	–
INJ-12 (Phase I)	74	Eprex/Erypo	s.c	–
2003-29-INJ-9 (pivotal Phase III)	Test: 314; Reference: 164	Erypo	i.v.	Therapeutic equivalence; mean absolute change in Hb level between the screening and/or baseline period and the evaluation period in patients with CKD undergoing haemodialysis
2003-31-INJ-11 (supportive Phase III)	Test: 74; Reference: 40	Erypo	s.c.	Absolute increase in Hb value of ≥2.0 g/dl between the screening and/or baseline period and the evaluation period in absence of red blood cell transfusion during the preceding 4 weeks

TABLE 3

Pharmacokinetic/pharmacodynamic and clinical studies for biosimilar product SB 309 (Epoetin zeta) marketed as Retacrit or Silapo

Study identification code	Subject number (enrolled)	Reference medicinal product	Route	Primary end point
411-54-05-05-0000 (Phase I)	24	Eprex/Erypo	i.v. 1 dose	–
411-54-03-09-0001 (Phase I)	48	Eprex/Erypo	s.c. and i.v. 1 dose	–
411-54-04-05-0000 (correction phase)	Test: 305; reference: 304	Erypo	i.v.	Weekly dosage of epoetin per kg body weight and Hb levels during the past 4 weeks of treatment
411-54-04-04-0000 (maintenance phase)	402	Erypo	i.v.	Intra-individual change (test-reference) in mean weekly dosage per kg body weight and Hb level of each product during the double-blind treatment period
411-54-04-14-0000 (additional maintenance treatment study)	745 (patients who completed correction or maintenance phase study)	n.a.	i.v.	Uncontrolled safety trial with particular focus on the formation of antiepoetin antibodies
441-54-04-46-0000	216	n.a.	s.c.	Uncontrolled safety trial on patients with cancer and chemotherapy-induced anaemia

literature. The guideline on similar medicinal products containing recombinant erythropoietins, which suggests that a pharmacodynamic study has to be performed, was not available at the time [17].

SB309 given i.v. was compared with the reference medicine in two main studies involving 922 patients with anaemia who were undergoing haemodialysis. The first study (411-54-04-05-0000) compared the effects of SB309 ($n = 305$) with those of Eprex/Erypo ($n = 304$) in correcting anaemia in 609 patients over 24 weeks. At the time of the evaluation period, Hb levels and the percentage of patients with treatment success were comparable in the two groups, but the SB309 dose was approximately 10% higher than that of the reference product. The second study (411-54-04-04-0000) compared the effects of SB309 with those of Eprex/Erypo in maintaining Hb levels in 313 patients in a 1:1 ratio (402 enrolled). Following a switch from the reference to the test drug, the dose increased by approximately 10–15%, whereas it behaved in the opposite way after a switch from test to reference product. The company also presented the results of a study looking at the effects of SB309 given s.c., which involved 216 patients with cancer receiving chemotherapy (411-54-04-46-0000).

Patients with renal anaemia completing either of the above efficacy studies were eligible to receive SB309 in an uncontrolled safety trial with particular focus on the formation of antiepoetin antibodies (411-54-04-14-0000), in which a total of 745 patients enrolled [17]. Following this study, in February 2010, the EMA gave its approval to the s.c. administration of SB309 in patients with CKD; therefore, the therapeutic indications are almost superimposable to those of Eprex.

Biopoin/Eporatio

Unlike HX575 and SB309, Biopoin and Eporatio are not biosimilars, but they were authorised with a full application. The MA holder had to submit complete modules 4 and 5. In the case of Biopoin/Eporatio (epoetin theta), which received MA in 2009, the company provided six Phase I pharmacodynamic/pharmacokinetic studies (Table 4), six Phase II/III studies supporting the indication of anaemia in patients with CKD, and three Phase III studies supporting the indication of anaemia in patients with cancer. In the setting of CKD, four separate studies enrolling 841 patients were undertaken to demonstrate the efficacy and safety of epoetin theta using the s.c. and i.v. routes of administration during both the correction and maintenance phase. The former were designed to demonstrate a dose-dependent average increase of Hb per week using fixed doses. As expected, the highest Epoetin theta group (120 IU/kg) had significantly higher Hb changes than the lowest one (20 IU/kg). In the maintenance phase studies comparing epoetin theta with epoetin beta, mean Hb values during the evaluation period were kept similar in both treatment groups and well within the chosen delta permitted, demonstrating noninferiority of epoetin theta to epoetin beta. Three Phase III studies in 586 patients with cancer receiving chemotherapy were also performed [18].

Following the submitted data, the approved therapeutic indications were limited to adult patients and to treatment of: (i) symptomatic anaemia associated with chronic renal failure in adult patients; or (ii) symptomatic anaemia in adult patients with non-myeloid malignancies receiving chemotherapy.

Clinical experience with epoetin biosimilars and epoetin theta

Today, the primary reason for prescribing a biosimilar is possibly its lower price. Indeed, these molecules are supposed to have similar efficacy and safety than their originators but lack possible advantages of newer molecules (i.e. less frequent administration schedule and dose equivalence between the s.c. and i.v. administration route). The pharmacological advantages of second- or third-generation erythropoiesis-stimulating agents [ESAs; e.g. darbepoetin alfa or continuous erythropoietin receptor activator (CERA)] might be relative in haemodialysis from the perspective of the patient, who regularly attend three treatment sessions every week. However, some advantages could be seen from the nurses' perspective, such as reducing their burden and possible mistakes of more frequent injections (risk management), avoiding the s.c.

TABLE 4

Pharmacokinetic/pharmacodynamic and clinical studies supporting the therapeutic indications of the innovative product Biopoin/Eporatio (epoetin theta)

Study identification code	Diagnosis and subject number	Route	Design and control type
XM01-12 (Phase I)	Healthy (18)	s.c. 3 doses	Open, randomised, three-way crossover
XM01-20 (Phase I)	Healthy (40)	s.c. 1 dose	Randomised, double-blind, placebo-controlled, parallel group
XM01-01 (Phase I)	End-stage renal disease (18)	i.v. 1 dose; s.c 2 doses	Open, sequential
XM01-11 (Phase I)	End-stage renal disease (14)	i.v. 7 doses over 2 weeks	Open, single group
XM01-10 (Phase I)	Chronic renal failure (14)	s.c. 7 doses over 2 weeks	Open, single group
XM01-24 (Phase I)	Non-myeloid malignancies (14)	s.c. 3 doses over 3 weeks	Open, single group
XM01-04 (Phase II); correction phase study	Anaemia associated with chronic renal failure, not yet receiving dialysis (133)	s.c.	Multinational, multicentre, randomised, controlled, double-blind parallel group; five groups with escalating doses of XM01-05, one group receiving epoetin beta
XM01-05 (Phase II); correction phase study	Anaemia associated with chronic renal failure, receiving haemodialysis (150)	i.v.	Multinational, multicentre, randomised, controlled, double-blind, parallel-group; four groups with escalating doses of XM01-05, one group receiving epoetin beta
XM01-06 (Phase III); maintenance phase study	Anaemia associated with chronic renal failure, not yet receiving dialysis (240; 159 Epoetin theta and 81 Epoetin beta)	s.c.	Multinational, multicentre, randomised, controlled, double-blind, comparative, parallel group; 2:1 randomisation ratio
XM01-07 (Phase III); maintenance phase study	Anaemia associated with chronic renal failure, receiving haemodialysis (224; 150 Epoetin theta and 74 Epoetin beta)	i.v.	Multinational, multicentre, randomised, controlled, double-blind, comparative, parallel group; 2:1 randomisation ratio
XM01-08 (Phase III)	Anaemia associated with chronic renal failure, not yet receiving dialysis (289)	s.c.	Open, multinational, multicentre, randomised, parallel-group; follow-up to XM01-04 and XM01-06
XM01-09 (Phase III)	Anaemia associated with chronic renal failure, receiving haemodialysis (124)	i.v.	Open, multinational, multicentre; follow-up to XM01-05
XM01-21 (Phase III)	Patients with solid tumours receiving platinum-containing chemotherapy and having a Hb level $\leq$11 g/dl (223)	s.c.	Multinational, multicentre, randomised, placebo- and active-controlled, double-blind, parallel-group study
XM01-22 (Phase III)	Patients with solid tumours or non-myeloid haematological malignancies receiving non-platinum chemotherapy and having a Hb level of $\leq$11 g/dl (186)	s.c.	Multinational, multicentre, randomised, placebo-controlled, double-blind, parallel group study
XM01-23 (Phase III)	Patients with low grade non-Hodgkin's lymphoma, chronic lymphocytic leukemia or multiple myeloma with endogenous erythropoietin deficiency receiving anticancer therapy and having a Hb level of $\leq$10 g/dl (amended to $\leq$11 g/dl) (177)	s.c.	Multinational, multicentre, randomised, placebo-controlled, double-blind, parallel group study

administration with the possible contamination risks just for economical reasons, and from the hospital perspective, reducing the organisational burden (e.g. re-ordering, the need for large storage space in refrigerators, among others). These advantages become more relevant in patients with CKD not receiving dialysis, and in patients undergoing peritoneal dialysis or who have received a transplant, in whom self-administration through the s.c. route is more probably. In these patients, less frequent treatment schedules could be a real advantage, reducing the illness perception, possibly increasing the safety, and reducing the possibility of breaking the cold chain of ESA preservation, so relevant for preserving the stability of ESAs, particularly when given s.c. Indeed, second- and third-generation ESAs are stable at room temperature for longer periods than are short-acting ESAs. These aspects should reduce the likelihood that biosimilars (and short-acting epoetins in general) are prescribed for these patients in the future (although, of course, price difference might have an important role in the decision). Given the use of the s.c. route of administration, these patients are more exposed to immunogenic risks following ESA administration. Even if SB309 can be administered both i.v. and s.c., only large, post-marketing studies will completely reassure physicians about the safety of biosimilars in terms of the risk of developing PRCA.

Depending on individual countries, biosimilar epoetins might offer an economical advantage compared with their originators. This is also true for epoetin theta, despite the fact that it did not go through the abbreviated registration procedure of biosimilars but was submitted to the EMA with a full dossier as an originator (and, thus, with a larger spend for clinical development). However, companies selling epoetin alfa and beta have lowered prices to remain competitive compared with biosimilars. The same has happened to darbepoetin alfa and CERA. Moreover, official prices might become significantly different when large quantities of the drug are bought by single, large organisations (e.g. hospitals or local health organisations) following a call for bids.

The equivalence in potency of the drugs should also be taken into account. The fact that biosimilars have been found comparable to originators in small studies made for EMA registration does not necessarily imply that similar efficacy is obtained with exactly the same doses. Indeed, the accepted range for therapeutic equivalence is wide (±0.5–0.6 g/dl for Hb; ±14 IU/kg/week for dosage). Small dose differences in the single patient could translate in substantial cost differences on a large scale. In a single dialysis centre, 18 patients treated with various ESAs were shifted to epoetin zeta [19]. After an observation period of 6 months, no significant changes were observed in Hb levels (11.72 ± 0.64 g/dl versus 11.62 ± 0.70 g/dl; $P = 0.64$). Similarly, changes in the mean weekly ESA dose were not statistically significant (from 5890 ± 4740 IU to 6890 ± 5312 IU; $P = 0.56$). However, this percentage dose increase of nearly 20% might become statistically significant in a larger sample size and might be economically relevant. Given that there was also a negative trend in Hb values, it is possible that the erythropoietin resistance index (i.e. the ratio between ESA dose and Hb) was statistically significant, but unfortunately this information is lacking from the study.

Conversely, Brinks et al. [20] recently compared the quality of four different epoetins, two original products: epoetin alfa (Eprex®) and delta, and two biosimilars: HX575 and epoetin zeta, using *in vitro* and *in vivo* techniques. They found that the biosimilars have the same or even better quality as the originators. Unexpectedly, epoetin alfa (Eprex) had a 129% higher potency than that declared on the package. Altogether, these considerations make economical evaluations of possible cost savings difficult following the entry of biosimilars into the EU market, other than a clear positive effect in reducing prices of all ESAs available on the market.

Despite their possible lower price, biosimilars still have limited diffusion in the EU market. This hesitancy might have several explanations. The first is the possible risk of inducing PRCA with a molecule that has not yet been used on a large scale. Second, the lower cost is to be balanced against possible advantages of second- or third-generation ESA. For the first time in the anaemia field, nephrologists are facing the problem of having new drugs with the same characteristics of the drug introduced in clinical practice more than 20 years ago.

Finally, shifting patients from one ESA to another might increase immunogenicity and reduce the possibility of identifying the culprit of the immunogenic reaction. This is the main reason why automatic substitution from an originator to a biosimilar is generally considered not acceptable. Automatic substitution at the dispensing level can be introduced by the Public Administration on the basis of interchangeability and is related to administrative procedures that can be implemented differently in different Member States. By contrast, interchangeability follows from therapeutic equivalence and is related to intrinsic drug characteristics. The originator drug and its biosimilar products (or biosimilar products from different manufacturers) are not interchangeable as bioequivalence cannot be used to demonstrate therapeutic equivalence, and the active substance is similar but not identical between the two products [13].

Consistently, a physician mainly prescribes epoetin biosimilars only to ESA-naive patients on haemodialysis. To widen the use of biosimilars and reduce treatment costs of patients with CKD, many hospitals and local health organisations in Italy have adopted the policy of making all types of ESA available for internal prescription, but require physicians to prescribe biosimilars in all ESA-naive patients who need treatment. Others have chosen to buy and prescribe only biosimilars. However, this approach is questionable, because physicians should be in charge of drug prescription for their patients and, thus, should have the responsibility of evaluating the cost:benefit ratio in each single patient.

Concluding remarks

Biosimilars are a current reality of the pharmaceutical market in the EU. The scenario is complicated by evolving regulatory policies, mainly established by guidelines issued by EMA, and periodically revised to reflect the experience gained.

Moreover, pharmaceutical companies can submit a given molecule with the characteristics of a biosimilar as a new application (presenting a full dossier) or as an abridged application, which makes the concept of 'biosimilarity' even more complicated. It is clear that in the latter case, the authorisation procedure is less taxing on the applicant both in terms of time and economics, because fewer clinical studies are required.

A comparison between the number and extent of studies needed to accompany the MAA for the different erythropoietins clearly shows the changes when the transition is made from an abridged to a full application. The companies applying for Biopoin/Eporatio had to provide more studies, although the number of subjects involved in a single study is often lower in the case of the originator, because there is no comparability exercise to be performed.

Biopoin/Eporatio has undergone six Phase I studies, both on healthy volunteers and on patients, against five (HX575) or two (SB309) Phase I studies on healthy volunteers in the case of the two biosimilars. The originator has undergone nine Phase II/III studies as opposed to two comparative studies for HX575 and four for SB309 (including two uncontrolled safety trials). Thus, it is clear that the biosimilar approach, when applicable, allows considerable time saving.

Manufacturers of reference and biosimilar products frequently make changes to manufacturing processes not only during development, but also after approval. Such changes might result in the evolution of a quality profile during the product lifecycle, so that the conclusion of a comparability exercise performed at a given time might not hold true for the whole lifecycle [21]. The actual impact of these changes on the product on the market has to be evaluated and a new comparability exercise might be required when the biotechnological active ingredient shows significant variations.

In addition, different products might cause different adverse events, particularly relating to immunogenicity, so that a specific pharmacovigilance policy is required. For example, a large, post-marketing, observational study about the use of HX575 in patients undergoing haemodialysis has recently been planned [22].

One final issue is that of substitution and interchangeability, where the term 'substitution' means automatic substitution at the dispensing level, without affecting the freedom of physicians to change a prescription on the basis of their knowledge and clinical data, under their own responsibility. Without the knowledge of the physician and patient consent, substitution should not be permitted, because in addition to clinical concerns, it could lead to difficulties in monitoring safety profiles of products compromising pharmacovigilance programs.

Conflict of interest

FL is a member of an advisory board of Affymax, Amgen-Dompè, Jansen, GSK, Roche, Takeda and of the safety board of Sandoz.

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