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Regulatory and clinical considerations for biosimilar oncology drugs

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Abstract

Biological oncology products are integral to cancer treatment, but their high costs pose challenges to patients, families, providers, and insurers. The introduction of biosimilar agents—molecules that are similar in structure, function, activity, immunogenicity, and safety to the original biological drugs—provide opportunities both to improve healthcare access and outcomes, and to reduce costs. Several international regulatory pathways have been developed to expedite entry of biosimilars into global marketplaces. The first wave of oncology biosimilar use was in Europe and

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Declaration of interests

The authors declare no competing interests.

India in 2007. Oncology biosimilars are now widely marketed in several countries in Europe, and in Australia, Japan, China, Russia, India, and South Korea. Their use is emerging worldwide, with the notable exception of the USA, where several regulatory and cost barriers to biosimilar approval exist. In this Review, we discuss oncology biosimilars and summarise their regulatory frameworks, clinical experiences, and safety concerns.

Introduction

Biological agents—biologicals—are integral to cancer treatment. They include cell therapies, cytokine or growth factors, monoclonal antibodies, and monoclonal antibody–drug toxin combinations; however, these drugs are expensive. In 2016, half of the ten most expensive pharmaceuticals will be biologicals.[1] Oncology biosimilars are complex pharmaceuticals that have similar molecular shape, efficacy, and safety to the original (so-called reference) biologicals. They have the potential to change oncology costs by offering low-cost alternatives to existing expensive cancer drugs,[2] but the patents and marketing exclusivities of oncology biologicals are expiring. Almost 40% of cancer therapies are biological, accounting for US$100 billion in sales.[3] In this Review we discuss the regulatory, economic, and clinical implications of oncology biosimilars.

Regulations

The regulation of biosimilars is evolving, with a trend towards international harmonisation, noted particularly between Europe and the USA. Guidances developed by the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and WHO set out principles for showing similarities between biosimilars and reference products (table 1). These require comparability for quality, efficacy, and safety assessments. In view of the complexity and cell-based production process, biologicals are inherently more difficult to characterise than standard pharmaceuticals. The EMA has the longest track record for assessment of biosimilars, which dates back to the 2003 EMA regulatory framework, and the initial EMA approvals of these products in 2006. US legislation for biosimilars was enacted in 2009.[12] Between 2008 and 2012, Canada, Australia, Japan, India, and South Korea adopted biosimilar regulations that are generally similar to EMA guidance. China and Russia currently regulate bio similars as new biological products, but are developing bio similar regulatory pathways.[13] Countries with emerging biosimilar industries, smaller regulatory agencies, or no regulatory pathway in place for bio similars generally allow extrapolation to indications for reference biologicals that have previously received approval.

Countries with established biological industries or regulatory pathways, or both

EMA guidelines lend support to an abbreviated pathway for biosimilar registration, with registration based on preclinical studies and clinical studies comparing efficacy, safety, and immunogenicity.[14–16] The reference biological has to have been authorised by the European Union (EU) for at least 10 years. Regulatory guidelines are customised for different biosimilar classes, such as epoetins or filgrastims.[17–19] Data requirements vary on a case-by-case basis.[20] EMA guidelines address manufacturing, non-clinical pharmacology, toxicology, pharmacokinetics, pharmacodynamics, and clinical considerations.

Pharmaceutical form, strength, and the administration route have to be the same as the reference products. Quality comparability and non-clinical toxicological findings should be tested. Clinical efficacy is assessed by pharmacokinetic and pharmacodynamics studies, followed by two-group or three-group clinical efficacy and safety studies. At least one equivalence trial, or a trial that includes the biosimilar, the reference biological, and a placebo, is required. Comparative studies should assess efficacy, safety, and immunogenicity. Postapproval pharmacovigilance and risk management studies are required, because many toxic effects are only detected after several years. EMA allows approval extrapolation to other indications on a case-by-case basis.

In the USA, the 2009 Biologics Price Competition and Innovation Act (BPCIA) set the FDA framework for biosimilar approvals.[21] Biosimilars cannot be approved until 12 years of market exclusivity for reference products have passed.[22] Indication extrapolation is possible on a case-by-case basis. The FDA will resolve comparability uncertainties using physiochemical and functional assays that assess changes in the manufacturing process, and preclinical and clinical studies.[20] The FDA has issued four draft biosimilar guidances from 2010 to 2014.[23,24] These outline approaches to the assessment of structure, function, and toxic effects in animals, the type of human pharmacokinetic and pharmacodynamics studies that will be sufficient to show safety, purity, and potency, and requirements for assessment of clinical efficacy, safety, and immunogenicity. The totality of the evidence will comprise risk-based assessments.[23,24] The FDA will consider protein complexity, manufacturing processes, studies comparing biosimilars with products that are licensed outside the USA, and postmarketing safety considerations. It has discretion to find out whether some elements of the regulatory procedure might not be needed. As of August, 2014, two Biologic Licensing Applications (BLAs) for biosimilars have been submitted via the 351(k) bio similars regulatory pathway.[25]

An EMA–FDA biosimilar cluster collaborative meeting helps with scientific exchange. The FDA is assessing lessons learned by the EMA about how a one-size-fits-all approach for all biologicals compares with developing class-specific guidelines, as the EMA did for filgrastim and epoetin.[18,19]

In Canada, guidelines were drafted by Canada Health in 2010 for subsequent-entry biologicals. These drugs are biologicals that enter the Canadian market subsequent to a biological version that has been previously authorised in Canada and shown similarity to a reference product. The guidelines were based on EMA guidelines, and will adopt drug class-specific guidance. Non-Canadian, licensed, reference products are allowed.[22] No oncology biosimilar has yet been approved in Canada.[26]

In Australia, the Australian Therapeutic Goods Administration (TGA) adopted EMA guidelines for biosimilar registration in 2008. Comparability data requirements are taken verbatim from the EMA and International Conference on Harmonisation guidelines, and rules on extrapolation abide by the guidelines from the EMA, but do not follow them verbatim.[22] The reference product has to be marketed in Australia. Australia has low levels of data protection for novel biologicals, with 5 years' exclusivity. Four oncology biosimilars are TGA-licensed— one epoetin and three filgrastims.[27]

Japan is the second-largest pharmaceutical market, after the USA.[28] Japan's Pharmaceutical and Medical Devices Agency's (PDMA) guideline for biosimilars was published in 2009, and is based on EMA guidelines. Unlike other countries, where licensing trials must be done in part or in total in the country where registration is being applied for, clinical trials supporting regulatory approval in Japan can be done in other Asian countries. The PDMA does not require clinical studies for biosimilar approval. In 2010, PDMA approved a biosimilar epoetin, although its indication does not include oncology; no oncology biosimilar has yet received PDMA approval.[29]

After the introduction of biosimilars in Europe in 2007, India established a second wave of introduction of biosimilars to its markets in 2007, although this was through a biological rather than a biosimilar approval pathway.[6] India is resource-challenged, with a semiregulated pharmaceutical industry and widespread income disparity; individual patients bear most of the pharmaceutical costs. The authority of the Central Drugs Standard Control Organization (CDSCO) is restricted to new drugs.[30,31] India developed regulatory approval processes for biosimilars in 2012, after approving 20 biosimilars via biological regulatory pathways. Patents are difficult to obtain, and expire earlier than in the USA and Europe. Interferon alfa-2b, filgrastim, pegylated filgrastim, darbepoetin, epoetin, and rituximab are marketed as biologicals.[6] Clinical trials for biosimilar regulatory approval require evidence of safety and biological equivalence, although formal requirements are less stringent than for the FDA or EMA. The reference product has to be licensed in India. Extrapolation to clinical indications for which the reference product has received CDSCO approval is not allowed.

South Korea is an attractive development venue for smaller Asia Pacific nations because the costs and time for obtaining regulatory approval are low. Regulatory biosimilar guidelines (2009) are based on guidelines from the EMA, WHO, and Japan. South Korea is second to the EU in terms of the number of marketed biologicals that have received regulatory approval via biosimilar-specific pathways. Biosimilar applications may be filed after approval of reference products, although this is difficult to do before 6 year re-examination periods of reference drugs (during which the drug's safety and efficacy profiles are assessed with postmarketing surveillance data). The type and amount of data required for biosimilar approval are established on a case-to-case basis. Biosimilars might receive extra polated authorisations if re-examination periods of reference products in these indications have expired.

Countries with emerging biological industries

Since 2010, several Latin American countries have developed biosimilar frameworks. Brazil, which has the most advanced framework, developed two approval pathways for comparable biological products that differ in the amount of data required for marketing approval.[13] The comparative pathway includes phase 1 pharmacokinetic and pharmacodynamics studies and phase 3 trials assessed on a case-by-case basis; extrapolation of indications is allowed after regulatory approval by this pathway. By contrast, for the individual development pathway, quality issues and clinical study requirements are lower, but extrapolation of indications is not allowed. Biosimilars will not be approved without

clinical data (as is done with so-called biocopies in Mexico). Colombia, Venezuela, and Mexico are developing guidelines.[32]

In China, about 40% of the biological market is for biosimilars. Cancer is the second most common cause of death in the country, and the use of biosimilar oncology drugs is growing. No specific biosimilar regulations are adopted by the China Food and Drug Administration (CFDA). Biosimilars are regulated as biological pharmaceuticals. The regulatory process for biological pharmaceuticals generally takes 6 years.[33] Regulatory applications for biosimilar oncology drugs, assessed as new biologicals, peaked in the late 1990s. Subsequently, these applications declined as large amounts of preclinical and clinical data were required. Some biosimilars are eligible for fast-track drug registration as a new pharmaceutical on a case-by-case basis. Specific biosimilar regulatory pathways are being developed by the CFDA.[34]

In 2013, international regulatory agencies, pharmaceutical manufacturers, and representatives of the Russian Ministry of Health convened a meeting on harmonisation of regulatory standards for Russian biologicals. Although Russia has a strong generics market, and an emerging biologicals market, Russia does not have a regulatory pathway for biosimilars. However, legislation formally defining biosimilars has been introduced, which initiated discussions about standards, interchangeability, and the choice of reference drugs for comparative assessments. Biosimilars are available in Russia for filgrastim, epoetin, and rituximab, although they are not approved by biosimilar regulatory pathways. The agents are interchangeable and substitutable by pharmacists with appropriate reference products that previously received Russian regulatory approval. Only biosimilar rituximab has gone through clinical trials in Russia.[35]

Naming

No international harmonisation on biosimilar naming exists (table 2). WHO guidelines advise that non-glycosylated biosimilars should have the same international non-proprietary name (INN) as the reference biological, whereas glycosylated biosimilars are noted with a Greek letter suffix (spelled out in full) added to the INN, as evident in the EU—eg, one epoetin biosimilar is named epoetin zeta.[36,37] The INN naming system remains voluntary. Australia and Japan further distinguish biosimilars from their reference products by adding unique prefixes or suffixes to the INNs. The EMA advises, but does not mandate, that biosimilars should share INN names with their reference drugs; unique names for the active substance are also assigned.[36]

The FDA has not adopted a naming position. The US Generic Pharmaceutical Association requests that biosimilars should share the same INN as the reference biological once comparability and interchangeability are shown.[38] Manufacturers of reference biologicals request that biosimilars marketed in the USA have unique INNs to help with adverse event tracking and reporting.[39]

Marketing

The amount of money spent globally on oncology reference biologicals in 2013 exceeded $32·4 billion. This included $8·9 billion for rituximab, $7 billion for bevacizumab, $6·8

billion for trastuzumab, $4·4 billion for pegfilgrastim, $2 billion for epoetin, $1·9 billion for darbepoetin, and $1·4 billion for filgrastim (table 3).[40,41]

EU biosimilar monitoring broadly tracks their historical generic use in individual countries. Biosimilar discounts range from 20% to 35% of the price of the reference product. Greece, Finland, and Germany are the largest users of biosimilar epoetins, and adopted these products earlier than other European countries. Greece and Italy are the largest users of biosimilar filgrastims. German insurance funds have biosimilar prescribing targets, because pricing for reference biologicals is high;[41] German physicians view biosimilars favourably, but their colleagues in other EU countries are less supportive. In some countries—eg, Finland and France—hospitals have financial incentives to adopt biosimilars, because they pay for in-hospital drugs but not outpatient ones, which are financed separately. Germany has established a reference pricing system and specific regional targets or quotas for physicians and sickness funds for biosimilar use. Spain has not adopted many biosimilars because prescribing decisions are made regionally by local physicians with strong connections to originator manufacturers.[41] The UK has adopted biosimilar filgrastim, but not biosimilar epoetin, mainly on the basis of differences in pricing with reference products.

Tbo-filgrastim, a product approved as a biosimilar in Europe, and in 2013 as a new biological in the USA, is discounted by 20% of the price of reference filgrastim. Despite this discount, its adoption in the USA is low. In China, biosimilars are priced 60% lower than reference products. This difference has enabled biosimilars to gain reimbursement from government insurance programmes and helped individuals unable to afford the originator products.[33] In India, before biosimilar rituximab approval, fewer than 1000 people received originator rituximab because of its high cost.[42] Since then, several thousand people have received biosimilar rituximab. In Russia, biosimilar rituximab approval and price discounts are expected, and therefore, presumably, overall use will increase. In Japan, biosimilars are priced at 70% of the reference products' prices. Based on these trends, manufacturers are optimistic that strong markets for biosimilars will subsequently arise.[28]

Substitution

In the EU, pharmacists' ability to automatically substitute biosimilars for reference biologicals is regulated nationally. Some countries have taken measures to limit or prohibit automatic substitution.[22] France is the first European country to explicitly allow biosimilar substitution.[43] In the legislation paralleling generic legislation, which would allow automatic substitution without prescriber intervention if the FDA deems that the biosimilar is interchangeable with reference products. Conversely, state-level legislation is being enacted that restricts automatic substitution—six US states have such laws.[44,45]

Safety

Manufacturing complexity and small differences between biologicals and related biosimilars lead to product-related, process-related, or host-related safety concerns. Therefore, novel comparative glycoprotein analyses should be developed that focus on preclinical immunogenicity assessments. Additionally, biosimilar manufacturers should undertake long-term pharmaco vigilance studies after biosimilar approval.[3,46]

Immunogenicity can lead to hypersensitivity, anaphylaxis, infusion reactions, and loss of efficacy. Immunogenicity can be induced by active-drug substance products, manufacturing impurities from changes in cell lines or media components, structural modifications, protein aggregation, suboptimum storage processes, and patient factors including human leucocyte antigen expression, comorbid conditions, and previous exposures.[47] An often-stated example of formulation changes resulting in immunogenicity is the substitution of polysorbate 80 and glycine for albumin as a stabiliser in the Eprex formulation of epoetin alfa, and the subsequent development of neutralising antibody-mediated, pure red cell aplasia (PRCA). Between 1998 and 2004, 175 cases of PRCA were associated with the Eprex formulation containing polysorbate 80. More than half of these cases were in France, Canada, the UK, and Spain. Between 2001 and 2003, the estimated exposure-adjusted incidence was 18 cases per 100 000 patient-years after subcutaneous Eprex. Pharmaceutical suppliers in Germany, Italy, Spain, and the UK adopted procedures ensuring the appropriate storage and handling of Eprex, and regulators in these countries mandated in 2002 that Eprex should be given intravenously to patients with chronic kidney disease. After these actions, the exposure-adjusted incidence of Eprex-mediated PRCA decreased to three cases per 100 000 patient-years, accounting for nine patients.[47] A second PRCA experience has been described—a clinical trial in Europe was discontinued after two patients with renal anaemia developed antibody-mediated PRCA after being given the subcutaneous epoetin biosimilar HX575.[48] Root-cause analyses suggested that tungsten contamination during manufacturing of prefilled syringes might have denatured proteins, and aggregation of HX75 occurred resulting in immunogenicity.[49] Biosimilar epoetin-associated antibody formation in Asia has also been reported. The first epoetin alfa biosimilar became available in 1997 in Thailand, and, in one study, 30 patients with chronic kidney disease who received subcutaneously injected biosimilar epoetin from Thailand developed loss of efficacy. Sera from 23 patients identified neutralising antibodies, and bone marrow biopsies suggested PRCA.[50]

Anaphylaxis is a safety issue identified with peginesatide, a dimeric erythropoietin-receptor agonist. The product was voluntarily removed from the US market in 2013, 1 year after receipt of FDA approval.[51] Overall, nearly 20 000 patients received peginesatide at 19 dialysis centres. Severe anaphylaxis, including five fatalities, occurred in 28 patients, accounting for 1·4 anaphylaxis or hypotension events per 1000 peginesatide-treated patients. Preservatives are being investigated for this issue, because after FDA approval, all peginesatide-treated patients received peginesatide from multiple-use vials with preservatives; however, in preapproval trials, peginesatide was given from single-use vials without preservatives.

A long-term safety concern is tumour stimulation by originator or biosimilar epoetins.[52–54] The FDA requires long-term pharmacovigilance studies focusing on tumour progression and survival for biosimilar epoetins that are being assessed for oncology indications. This requirement has resulted in manufacturers pursuing FDA approvals for epoetin biosimilars for chronic kidney disease indications only.

Another long-term safety concern is associated with filgrastim. The reference product has been used for mobilisation of peripheral blood stem cells from healthy donors. Possible

long-term safety concerns regarding filgrastim have been raised, including activation of autoimmune diseases, and epigenetic or genetic changes that might lead to haematological malignancies.[55–57] The European Group for Blood and Marrow Transplantation, the World Marrow Donor Association, several Italian Societies and Groups, and the Japan Society for Hematopoietic Cell Transplantation advise that biosimilar filgrastim should not be given to healthy donors outside clinical trials or long-term registries.[57–61] Conversely, the European Working Party on Similar Biological Products reports that all biosimilars should be considered biologically similar after they receive EMA approvals that assess comparability, because of the rigour of these processes.[62]

A black triangle symbol on the product information for a medicine or vaccine in the EU shows that the product is subject to additional safety monitoring. This scheme, adopted in 2013 across the whole EU, had been a longstanding programme in the UK.[63,64] The drugs list for black triangles is agreed Europe-wide and includes EMA-approved biosimilars. The black triangle symbol is generally maintained for 5 years for a product, and during that time, any suspected side-effect associated with the medicine should be reported to that country's medicines regulatory agency. No biosimilars at this time carry a black triangle symbol.

Because of a shortage of data for immunogenicity, the manufacturers of biosimilars that receive EMA approval for indications not studied in regulatory phase 3 trials of the biosimilars (ie, extrapolation indications) must undertake post marketing pharmacovigilance studies of whether clinically significant antibodies occur in these settings, and if these have clinically relevant effects. Europe has the longest track record for safety assessments of biosimilar epoetin and filgrastim. Annual periodic safety update reports for these drugs have not identified differences between biosimilars and reference products in frequency, type, or severity of adverse events. Results from EMA-required postapproval risk management plans are immature. A biosimilar epoetin zeta safety study was done in four European countries.[65] Overall, 1634 anaemic patients with chronic kidney disease receiving haemodialysis were given biosimilar epoetin intravenously for up to 1 year. Serious adverse events included 105 thromboembolic events (6·4%), 30 cerebrovascular events (1·8%), and 160 events of clotting of the artificial kidney (9·8%), but there were no reports of PRCA, neutralising antibodies, anaphylaxis, or angio-oedema. The manufacturer is doing a postauthorisation, 3-year observational study investigating biosimilar epoetin zeta given by subcutaneous injection to 6700 European patients with anaemia associated with renal disease (trial registration number PMS-830-09-0082). For biosimilar filgrastim, interim results from 200, healthy, unrelated donors suggested that the acute-phase safety profile was consistent with known toxic effects of the reference product and no splenic ruptures happened.[66] This study will contribute up to 10 years of safety data for 2000 person-years.

The FDA will study the immunogenicity of biosimilars in a risk-based manner. The use of premarket versus postmarket testing will vary depending on expected risks, analytical similarity between products, and incidence and clinical results of immune responses. If reference products are therapeutic counterparts of endogenous proteins with crucial, non-redundant, biological functions, or are known to provoke anaphylaxis, detailed immunogenicity studies will be required. If immune responses to reference products are rare, then a premarket study powered to detect major differences in immune responses

between products and a postmarket study designed to detect more subtle immunogenicity differences will suffice.[3] Safety monitoring will be product-specific because pharmaceutical companies periodically make manufacturing-related changes and small changes can affect safety or efficacy. Differentiating the adverse events related to the reference product from those related to the biosimilar needs a record of the product brand name, manufacturer, and batch number. According to the BPCIA, biosimilars could meet a higher standard of similarity with reference products, allowing interchangeability by physicians if the biosimilar is expected to produce the same clinical results as reference products, and if there is no greater risk of safety or diminished effectiveness. The risk evaluation and mitigation strategy established for reference products should be undertaken for related biosimilars.[3]

Specific biosimilars

Filgrastim is marketed widely for neutropenia prevention in patients with non-myeloid cancer receiving chemotherapy.[49] It is a small protein, without additional modifications, and is readily produced by *Escherichia coli.* Biosimilar filgrastim was first given regulatory approval as a biological in India in 2001, and then in Europe in 2006 as a biosimilar. Seven biosimilar filgrastims are EMA-approved.[67–74] The EMA accepted the manufacturers' proposals that minimally clinically important differences between a biosimilar and the reference filgrastim product were the difference of more than 1 day of severe neutropenia after myelosuppressive therapy.[67–74] Biosimilar filgrastim received extrapolated approval for peripheral blood stem cell mobilisation, chronic, cyclic, or difficult-to-treat neutropenia, and peripheral blood stem cell mobilisation. Two biosimilars differ from the reference product with respect to buffer systems. Four phase 1 pharmacokinetic and pharmacodynamic studies were undertaken with healthy volunteers.[67] One phase 3 study of patients with breast cancer suggested that commonly reported drug-related adverse events—bone pain, asthenia, and myalgia— occurred equally often with biosimilar filgrastim and reference filgastrim, and that high immunogenicity rates with the biosimilar version were unlikely.[67] Another biosimilar filgrastim is unglycosylated, and contains an N-terminal methionine. Two pharmacokinetic and pharmacodynamics phase 1 studies were done with healthy volunteers and showed similar activity to the biological. One phase 3 trial of patients with breast cancer supported therapeutic equivalence between the biosimilar and biological for both mean absolute neutrophil count nadirs and time to absolute neutrophil recovery. No unexpected toxic effects, including immunogenicity, were identified with postapproval studies done since 2008. Manufacturers of two EMA-approved biosimilar filgrastims voluntarily withdrew regulatory approvals for business reasons. XM02 is a biosimilar filgrastim associated with four EMA-approved biosimilar filgastrims. EMA approval was based on six primary pharmacodynamics studies, one secondary pharmacodynamics study, two pharmacokinetic studies, six toxicology studies, two phase 1 studies, and three phase 3 studies. The phase 1 studies compared the biosimilar serum concentrations and CD34+ cell count peaks at 72 and 336 h with the reference product. Efficacy was assessed on the basis of three randomised trials of patients with breast cancer, lung cancer, or non-Hodgkin lymphoma. No significant differences in mean absolute neutrophil counts nadir and time to absolute neutrophil count recovery were noted. XM02 received US FDA approval in 2012 as tbo-filgrastim via a BLA pathway. A 12-year marketing exclusivity was granted versus

12–42 months that would have been granted with the biosimilar pathway approval. Two phase 1 studies included pharmacokinetic and pharmacodynamics assessments of 200 healthy volunteers receiving XM02 or filgrastim. Phase 3 studies were assessed by the FDA and EMA for approval. In pooled analyses, no clinically relevant differences between XM02 and filgrastim were noted. The FDA concluded that XM02 was better than placebo for minimisation of severe neutropenia duration in the first cycle of treatment, had no unanticipated or significant safety signals, and that its benefit–risk profile was favourable. FDA approval allows marketing of XM02 for the indication assessed in pivotal trials (prevention of febrile neutropenia after chemotherapy) and it does not require postapproval pharmacovigilance studies.[75] In 2014, the National Comprehensive Cancer Network's revised guidelines recommended that either tbo-filgrastim or filgrastim can be given prophylactically for febrile neutropenia if the risk of chemotherapy-associated febrile neutropenia is greater than 20% and if equally effective treatments that do not need granulocyte-colony stimulating factor support are unavailable. Tbo-filgrastim is 20% cheaper than filgrastim.[76]

Epoetin alfa received FDA approval to treat anaemia and reduce the need for transfusions in patients with cancer receiving chemotherapy, and patients with chronic kidney disease.[62] Because epoetin needs glycosylation for stability and activity, mammalian Chinese hamster ovary host cells were chosen for production of epoetin biosimilars. Five epoetin biosimilars received EMA approval.[77–81] The EMA accepted proposals from the biosimilar manufacturers that clinically important differences would be a 95% CI of more than 5 g/L for the difference in mean absolute haemoglobin change. EMA-approved epoetins have the same mechanisms of action, although pharmacological properties differ. Most approvals of these products were based on the demonstration of comparability with Eprex as a reference product, a formulation marketed in countries outside the USA. Epoetin biosimilars differ in their degree of glycosylation, which affects their pharmacokinetics, pharmacodynamics, effectiveness, safety, and immunogenicity. HX575 is an epoetin alfa biosimilar with the same aminoacid sequence as its reference product. Its structure contains more phosphorylated, high mannose-6-phosphate glycans and lower concentrations of N-glycolylneuraminic acid and diacetylated neuraminic acids than Eprex. EMA approval of HX575 was restricted to intravenous administration, on the basis of phase 3 studies (479 patients with chronic kidney disease and 114 patients with cancer).[82–84] An epoetin zeta biosimilar has a backbone structure that is similar to epoetin alfa, but contains slightly more glycoforms. Biosimilar epoetins are available in many countries. Three phase 3 trials of epoetin alfa in the chronic kidney disease setting in the USA are complete, and results are pending (trial numbers NCT01170078, NCT01473407, and NCT01473420).

Darbepoetin has additional synthetic glycosylations relative to epoetin, is designed to improve biostability, and was approved by regulatory agencies to be given every 3 weeks.[84] Biosimilar darbepoetin, manufactured by an Indian pharmaceutical manufacturer, was approved in India in 2010 for transfusion in patients with chronic kidney disease and cancer patients receiving chemotherapy.[85]

Biosimilar rituximab, an antiCD20 monoclonal antibody approved for non-Hodgkin lymphoma, chronic lymphocytic leukaemia, and several immunological diseases, is the first

oncology therapeutic biosimilar to receive regulatory agency approval internationally. In a single-group clinical trial of 67 patients with non-Hodgkin lymphoma, 63 (94%) of patients achieved an overall response with biosimilar rituximab, similar to that reported for the reference product.[42] Benefit-versus-risk assessments were based on similar proportions of patients achieving a response and toxic effects compared with historical data. The rituximab biosimilar is marketed in Bolivia, Chile, and Peru. Continuing biosimilar studies are being done by two other pharmaceutical manufacturers in India, and several biosimilar formulations are being assessed in Argentina, Belarus, Brazil, France, Germany, India, Spain, and Turkey. Phase 3 trials of rituximab biosimilars undertaken by other manufacturers were discontinued because of concern that patent litigation would be initiated by the originator's manufacturer.[86,87] In 2014, biosimilar rituximab was approved in Russia for non-Hodgkin lymphoma treatment based on a clinical study comparing pharmaco kinetics, pharmacodynamics, safety, and efficacy versus the reference product. The trial was done at 30 centres in India, Russia, South Africa, and Ukraine.

Trastuzumab is a biological drug approved to treat aggressive HER-2-positive, metastatic breast cancer, and HER2-positive metastatic or locally advanced gastric adenocarcinomas. In 2013, a South Korean manufacturer reported a phase 3 trial showing that 138 (57%) of 244 patients achieved an overall response for biosimilar trastuzumab and paclitaxel, similar to those treated with the reference trastuzumab and paclitaxel (143 [62%] of 231 patients) for women with metastatic breast cancer.[88] In 2014, the South Korean Ministry of Food and Drug Safety granted regulatory approval for a trastuzumab biosimilar for the same indications as the reference product on the basis of phase 1, 2, and 3 clinical trial data for 558 women with breast cancer at 115 sites in 18 countries.[88,89] In 2013, a generic drug maker in India received regulatory approval for a similar biological version of trastuzumab. The manufacturer of the trastuzumab originator product had abandoned its patent for the innovator, purportedly in response to anticipated governmental issuance of a compulsory licence for trastuzumab because of inaffordability.

The VEGF antibody bevacizumab received regulatory approvals for treatment of cancers of the colorectum, brain, non-small-cell lung, and renal system. Plans to manufacture a biosimilar bevacizumab were announced in 2012 by several manufacturers. In 2013, an Indian generic drug maker and its partner received regulatory approval to market biosimilar bevacizumab in India.

Conclusions

International biosimilar markets could be worth about $20 billion by 2020, with oncology sales accounting for most of this market. Quality, safety, and efficacy of these drugs in the oncology setting should therefore be addressed. In view of the high costs of cancer biologicals, many countries pin their hopes on biosimilars to bend the oncology-cost curve —ie, to reduce otherwise high costs in this specialty. Oncology biosimilar use has increased in some European countries. However, in the USA, there are many regulatory and legal obstacles to widespread use of biosimilars. These obstacles, not noted previously with generic cancer pharmaceuticals, include high development costs, expectations of small price discounts, legal policies that restrict substitution, uncertain acceptance by providers and

patients, requirements for clinical trials to be larger than those needed for generics, and market-exclusivity periods of 12 months versus 12 years if the BLA pathway is used.[90] In other countries, favourable financial, market, and regulatory climates exist. Overall health-care costs could rise if these products are sold more at low costs and use increases dramatically. Finally, a safety issue such as unexpected cases of PRCA, anaphylaxis, tumour progression, or haematological malignancies with European or US biosimilars will also broadly hinder uptake.

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Search strategy and selection criteria

Data sources included reports from regulatory agencies, WHO, product manufacturers, and English-language publications from the Ovid, PubMed, Cochrane, and Lexus Nexus databases, published between Jan 1, 2003 and Oct 30, 2014 (search terms: “biosimilars”, “biologicals”, “follow-on biologics,” “similar biologic products”, “subsequent entry biologics”, “follow-on biologic products”, and “similar biologic medicinal products”).

Table 1

Comparison of biosimilar guidelines between countries

	Europe	USA	India	Latin America	South Korea	Australia	Canada	Japan
	Directive 2001/83/EC—implemented by the EMA's Committee for Medicinal Products for Human Use[4]	Biologics Price Competition and Innovation Act of 2009 (BPCIA)[5]	Guidelines on similar biologics: regulatory requirements for marketing authorisation in India[6]	Regulation of SBPs in Latin America varies substantially across countries. Although the process is still in flux, the region is moving in the direction of more rigorous oversight of SBPs. Generally, Latin American countries tend to adopt guidelines on the basis of accepted international standards[7]	Guideline on evaluation of biosimilar products (July, 2009)[8]	Therapeutic Goods Act 1989. Australia's guidelines are based on the EMA's pathway, and include some verbatim language from the EMA's guidelines[9]	Guidelines for SEBs; adopted March, 2010)[10]	Guidelines for the quality, safety and efficacy assurance of follow-on biologics (Yakushoku shinsahatu 0304007 by MHLW; March 4, 2009)[11]
Regulatory authority	EMA	FDA	The Central Drugs Standard Control Organization and Department of Biotechnology	..	Ministry of Food and Drug Safety, formerly the Korean Food and Drug Administration	Therapeutic Goods Administration	Therapeutic Products Directorate of Health Canada	MHLW
Definition	A biological medicine similar to another biological medicine that has already been authorised for use	A biological product highly similar to the reference product notwithstanding minor differences in clinically inactive components	A biological product or drug produced by genetic engineering techniques and claimed to be similar in terms of safety, efficacy, and quality to a reference biological	..	A biological product shown to be comparable, in terms of quality, safety, and efficacy, to a reference drug	Similar biological medicinal product from the EU guidelines	A biological drug that enters the market subsequent to a version previously authorised in Canada with demonstrated similarity to a reference product	A biotechnological drug product developed by a different company, which is comparable with an approved biotechnology-derived product
Reference product	Has to be authorised in the EU on the basis of a complete dossier	Has to be licensed with a full biologicals licence	Only a biological product that was licensed on the basis of a full	..	The reference drug is used in demonstrating the	The reference product has to be approved in Australia and marketed for a suitable duration and have a volume of marketed	A biological drug authorised on the basis of a complete quality, non-	The reference products should be drugs that are approved in

	Europe	USA	India	Latin America	South Korea	Australia	Canada	Japan
		application. Section 351(a) of the Public Health Service Act outlines the reference product characteristics	351(a) of the Public Health Service Act outlines the reference product characteristics	351(a) of the Public Health Service Act outlines the reference product characteristics	comparability exercise that is likely to be a substantial body of acceptable data regarding the safety and efficacy through quality, non-clinical, and clinical studies	reference product characteristics	clinical, and clinical data package	Japan and be the same product throughout the development period of the biosimilar products
Non-clinical data	Non-clinical studies should be comparative and designed to detect differences in responses between the biosimilar and the reference product	Generally, an application should include data derived from animal studies to help to show that the product is biosimilar to a reference product	In-vitro cell-based bioassays or animal studies should be used to establish comparability of the biosimilar and the reference product	..	Non-clinical studies could be done with methods such as assays in vivo, PK/PD, and studies of toxic effects, to establish the comparability of the biological or PD activity between the reference and biosimilar product	See EU guidelines	Non-clinical data include: in-vitro and in-vivo studies, PD studies, a repeat-dose study of toxic effects, and other relevant safety results	Non-clinical studies include PK, pharmacological studies, studies of toxic effects, and local tolerance
Clinical trials	Comparative efficacy clinical trials are generally needed to show clinical comparability. A biosimilar's immunogenicity should be studied. Immunogenicity risks in different indications should be considered	Generally, an application has to include data derived from a clinical study or studies that are sufficient to show safety, purity, and potency in one or more appropriate conditions of use	Comparative clinical trials, including PK/PD, to show the similarity in safety and efficacy of the similar biological and reference biologicals are required	..	The clinical comparability studies include PK/PD, and efficacy studies	See EU guidelines	Clinical studies include PK/PD studies, and clinical efficacy and safety trials	Clinical studies include PK/PD studies, with the appropriate PD marker. Clinical safety studies (immunogenicity) should be considered

	Europe	USA	India	Latin America	South Korea	Australia	Canada	Japan
Extrapolation	Extrapolation to other diseases and settings for which reference products have EMA approval is on a case-by-case basis	Indication extrapolation is possible on a case-by-case basis	A similar biological can be extrapolated to other clinical applications in some circumstances, such as when similarity in quality or preclinical assessment has been established between the biosimilar and the reference product	..	In some circumstances, a biosimilar product might receive extrapolated authorisation for other indications of the reference product	The guidelines adopt the same standards of extrapolation as the EU	Clinical data could be extrapolated to other indications for which rationales are sufficiently persuasive	Extrapolation to other indications of the reference product might be possible
Naming and labelling	Commercial name, appearance, and packaging should differ and INN should be the same for related biosimilars	Not yet addressed; discussion is ongoing	Biosimilars require unique INNs to help with prescripion and dispensation of biopharmaceuticals, and support rigorous pharmacovigilance	..	Not addressed	A biosimilar's Australian Biological Name must include the active ingredient of the reference product, and a biosimilar identifier. The biosimilar's trade name must be clearly distinguishable from the reference product. This system differs from the EMA and WHO	The labelling (product monograph) for an SEB should be developed in consistency with the principles, practices, and processes outlined in the Guidance for industry: product monograph (2004)	The non-proprietary name of a biosimilar in Japan includes a name for the generic combination and refers to the name of the reference product
Pharmacovigilance	A risk management pharmacovigilance plan must be submitted for biosimilars. Clinical safety has to be monitored closely after marketing authorisation for biosimilars	Any existing risk evaluation and mitigation strategy for the reference product applies to biosimilars. FDA could mandate postmarketing studies, clinical trials, or labelling changes for biosimilars	The applicant must submit a postmarketing risk management plan, reports of adverse drug reactions within 15 days of initial receipt, and at least one postmarketing safety and immunogenicity study	..	Pre-authorisation safety data should be done (with sufficient power) to assess the safety profile of the biosimilar	Postregistration pharmacovigilance is the same as for novel biologicals	A risk management plan should be submitted before the issuance of marketing authorisation, and should include periodic safety update reports. Any serious adverse drug reactions has to be reported within 15 days	Postauthorisation studies of the clinical safety of biosimilar products should be done and monitored on a continuous basis
Substitution	Substitution is determined at the member-state level, and therefore this topic is not directly addressed in EMA guidance	Interchangeable—the applicant has to show that the biological product can be expected to produce the same clinical result as the reference product in any patient.	Biosimilar substitution is automatic as soon as it is approved	..	Not addressed	No automatic substitution	No automatic substitution	Substitution should be avoided during the postmarketing surveillance period

	Europe	USA	India	Latin America	South Korea	Australia	Canada	Japan
	Biosimilars that are deemed interchangeable could be substituted for reference products without physicians' orders	Biosimilars that are deemed interchangeable could be substituted for reference products without physicians' orders	Biosimilars that are deemed interchangeable could be substituted for reference products without physicians' orders	Biosimilars that are deemed interchangeable could be substituted for reference products without physicians' orders	Biosimilars that are deemed interchangeable could be substituted for reference products without physicians' orders	Biosimilars that are deemed interchangeable could be substituted for reference products without physicians' orders	Biosimilars that are deemed interchangeable could be substituted for reference products without physicians' orders	Biosimilars that are deemed interchangeable could be substituted for reference products without physicians' orders

EMA=European Medicines Agency. SBP=similar biotherapeutic products. MHLW=Ministry for Health, Labour, and Welfare. PK=pharmacokinetic. PD=pharmacodynamic. SEB=subsequent entry biological. EU=European Union. INN=international nonproprietary names. FDA=US Food and Drug Administration.

Table 2

Reference products with corresponding oncology biosimilars approved by a biosimilar regulatory pathway*

	Biosimilar	Year of approval	Lead biosimilar in development	Other biosimilars in development
Epoetin† (FDA expiration—2013; EMA expiration—2006)	Abseamed	EU 2007	..	..
	Binocrit	EU 2007		
	Epoetin alfa hexal	EU 2007		
	Retacrit	EU 2007		
	Silapo	EU 2007		
Filgrastim (FDA expiration—2013; EMA expiration—2006)	Biograstim	EU 2008	..	..
	Filgrastim hexal	EU 2009		
	Filgrastim	EU 2008; marketing approval voluntarily withdrawn by manufacturer in EU		
	Ratiopharm	EU 2013		
	Gastofil	EU 2010		
	Nivestim	EU 2008		
	Ratiograstim	EU 2008		
	Tevagrastim	EU 2009		
	Zarzio	Australia 2013		
Bevacizumab (FDA expected expiration—2019; EMA expected expiration—2022)	..	India 2013	Amgen or Actavis, and Biocad—both in late-stage clinical trials	..
Darbepoetin (FDA expected expiration—2024; EMA expected expiration—2016)	..	..	Pending regulatory approval in Albania, Bosnia, Bulgaria, Croatia, Cyprus, Greece, Kosovo, Macedonia, Montenegro, Romania, Slovakia, Slovenia, and Serbia	..
Rituximab (FDA expected expiration—2018; EMA expiration—2014)	..	India 2013	Amgen—in phase 3 trial in 2013	Boehringer Ingelheim in phase 3 trials for rheumatoid arthritis and phase 1 for lymphoma; Merck—phase 3 trials—active but not recruiting NCT01390441 and NCT01370694; Sandoz—phase 3 trials in the USA
Trastuzumab (FDA expected expiration—2019; EMA expiration—2014)	..	India 2013 South Korea 2014	Amgen—pivotal trial launched in 2013; Biocad—late-stage clinical trial; Hospira—expected to submit for EMA approval in 2014	Pfizer—in phase 3 trials (REFLECTIONS B327-02; NCT01989676)

FDA=US Food and Drug Administration. EMA=European Medicines Agency. EU=European Union.

*Biosimilar regulatory pathways were established in the EU in 2006, in the USA in 2009, in Japan in 2009, in South Korea in 2009, in Canada in 2010, and in India in 2012.

† Epoetin alfa brand names: Abseamed, Binocrit, and Epoetin alfa hexal; epoetin zeta brand names: Retacrit and Silap.

Table 3

Market share for oncology biosimilars relative to the innovator product in European Union countries in 2009*

	Filgrastim	Epoetin
Widespread use of either filgrastim biosimilar, or epoetin biosimilar, or both		
Greece	100%	71·9%
Italy	56·5%	0·3%
Finland	0·0%	54·6%
Germany	14·5%	53·0%
Latvia	43·4%	0·0%
Lithuania	34·0%	0·0%
Romania	22·0%	10·8%
Sweden	4·5%	21·2%
Austria	20·7%	20·2%
United Kingdom	20·0%	1·0%
No widespread use of either filgrastim biosimilar or epoetin biosimilar		
Poland	0·2%	16·8%
Norway	12·4%	2·8%
Spain	6·6%	2·9%
Hungary	6·3%	4·0%
Switzerland	5·3%	0·6%
Other		
France	4·5%	3·0%
Netherlands	2·2%	0·4%
Slovakia	0·3%	2·0%
Ireland	0·1%	0·3%
Bulgaria	0·1%	0·0%
Belgium	0·0%	0·0%
Denmark	0·0%	0·0%
Portugal	0·0%	0·0%

*Market data and analyses performed by Rovira and colleagues,[41] who obtained data from IMS Spain and the MIDAS database.