Biopharmaceuticals are complex protein molecule drugs produced by living organisms. Biopharmaceuticals as anti-neoplastic monoclonal antibodies are a major breakthrough in oncology. When the patent of innovator biopharmaceuticals expires, copies will be introduced. These copies are after approval by European Medicines Agency (EMA) within EU called biosimilars and have their own regulatory pathways which differ from the chemical generics approval process. The main reason is that identical copies of chemical molecules via chemical syntheses can be produced but copies of innovator biopharmaceuticals will only be similar. An extensive comparability exercise has to be carried out between the reference product and the biosimilar before approval. However, still there might be differences between the innovator anti-neoplastic monoclonal antibody and the biosimilar anti-neoplastic antibody which cannot be detected until extended clinical studies have been carried out. Moreover, all indications for an anti-neoplastic biosimilar antibody may not have been tested for at the time of approval but extrapolated based on the indications of the reference monoclonal antibody. The limited information on biosimilar anti-neoplastic monoclonal antibodies at approval may still be justified taking into account that the aim is to reduce price. However, the risk–benefit ratio for biosimilar anti-neoplastic monoclonal antibodies should be carefully evaluated, considering that anti-neoplastic monoclonal antibody therapy has a curative intent, price reduction so far within EU of biosimilars is modest and that in the end only part of the total costs for cancer health care is related to biopharmaceuticals.

**Key words:** biosimilar, monoclonal antibodies, oncology

**introduction**

Small chemical molecule drugs as chemotherapeutics/cytotoxic drugs comprise most pharmaceutical drugs developed via chemical synthesis. Cytotoxic chemical generics are identical or within an acceptable bio-equivalence range to the brand-name counterpart with respect to pharmacokinetic (PK) and pharmacodynamic properties. Chemical generics are considered identical in dose, strength, route of administration, safety, efficacy and intended use. When the patent expires for chemical cytotoxic drugs, the manufactures of the off-patent drugs have to show bioequivalence to the innovator drug not including toxicology and clinical efficacy trials. Similar rules are applied both by EMA (European Medicines Agency) and by Food and Drug Administration.

The aim of introducing chemical cytotoxic generics is practically only price reduction to lower the costs for oncologic health care. As cytotoxic generics are bioequivalent to the innovator drugs, the market introduction of such drugs should be of no clinical concerns although post-marketing pharmacovigilance programs have to be the same as for the innovator drugs.

Biopharmaceuticals (including protein and carbohydrate derived drugs) are medical products whose active drug substance are made by living organisms, exhibiting high-molecular complexity and are sensitive to changes in the manufacturing processes. Several biopharmaceuticals in oncology have reached a block-buster status, i.e. annual sales of more than US $ 1 billion. From an economic health care perspective, it should be of interest to produce and introduce off-patent drugs when the patent expires to reduce oncology health care costs.

**terminology**

EMA early realized that the chemical generic pathway for drug approval was not applicable for biopharmaceuticals and hence, a biosimilar approval pathway was implemented in 2005 [1]. Previously, the term biogenerics has been used for non-innovator off-patent biopharmaceuticals, but the term biogenerics should be disregarded as it may give the impression of identity in accordance with the concept for chemical generics. The term biogenerics is still in use above all in developing countries. According to the EU, a biosimilar medical product is a copy version of an already authorized biological medicinal product (the reference product) with demonstrated similarity in physicochemical characteristics, efficacy and safety based on a comprehensive comparability exercise [1, 2]. However, because of the inherent variability of biological systems used for...
manufacturing, the resulting biological products will display a certain degree of variability.

Synonymous to biosimilars are ‘similar biotherapeutic products’, ‘subsequent-entry biologicals’ and ‘follow-on biologicals’. ‘Me-too biologic’ or ‘biocopy’ are biological medicinal products developed on its own and not directly compared and analyzed against a licensed reference biological. These types of biopharmaceuticals are in use in developing countries. ‘Second-generation biologicals’ or ‘biobetters’ are biologicals that have been structurally and/or functionally modified to achieve and improve a different clinical performance. Those drugs have usually a stand-alone development with a full developmental program. From a regulatory perspective, the claim for better has to be substantiated by data showing clinical advantages over the previous generation product [3]. Such examples are filgrastim compared with pegfilgrastim or darbepoetin alfa compared with epoetin alfa.

**patent expiration**

In oncology, biosimilars have been in use for several years for supportive care. Epoetin alfa and filgrastim were the first to be approved. The uptake of those biosimilars in the European market has been slow which may at least partly be attributed to a lack of trust in the efficacy and safety of biosimilars as well as their interchangeability with the originator product by both patients and clinicians [4]. In the case of biosimilar epoetin alfa, it might be added that epoetin alfa is usually given during a long time for anemia correction with the risk for antibody induction and subsequent development of pure red cell aplasia. This is a serious adverse event. Treating physicians are aware of the risk and might therefore prefer to use a drug with a documented long-term experience in a large number of patients. In the case of biosimilar filgrastim, there seems to be a higher acceptance and the uptake is increasing (Figure 1), which might be attributed to the indications for the use of filgrastim. Eighty-five percent of all the use of filgrastim is for chemotherapy-induced neutropenia (CIN). For this indication, the treatment period is short and given to immune suppressed patients, which have a low risk of developing anti-filgrastim antibodies and subsequent related side-effects. Moreover, filgrastim seems to be less immunogenic than epoetin.

There is still a reluctance among hematologists and oncologist to use biosimilar filgrastim for the treatment of healthy donors for harvesting of hematopoietic stem cells and for the long-term therapy of patients with chronic neutropenia [5]. The last two indications are extrapolations, i.e. no clinical documentations were submitted with the application dossiers but according to the regulation, extrapolation is allowed, provided that the mechanisms of action are the same. Treatment of healthy individuals and long-term therapy are, however, not the same as CIN. Unexpected side-effects might be seen in these populations treated with biosimilars, but not in CIN and not with the innovator drug as subtle product differences may have clinical consequences. The full safety and efficacy profile cannot be answered satisfactorily until large populations with these indications have been treated and followed up for a long time.

Biosimilar monoclonal antibodies for tumor therapy (antineoplastic monoclonal antibodies) have not yet reached the market. The first patent to expire is rituximab with expiry dates in Europe of November 2013 and in the United States September 2016 (Figure 2). The expiry dates for other biopharmaceuticals in use in oncology are also shown in Figure 2.

Both rituximab and trastuzumab biosimilars are in a clinical developmental phase. Market authorization of rituximab biosimilar for oncology in Europe might, however, not occur until 2015. Rituximab biosimilar programs in inflammatory disease and oncology have been initiated. However, during autumn 2012 it was announced by Samsung and Teva that the rituximab biosimilar programs were halted due to some uncertainty of the guidelines for market authorization in the Asian markets.

Biocopies of rituximab are already marketed in Central and South America and in several countries in Asia. Although bioscopies do not fulfill the criteria for approval according to EMA requirements, it should be of great clinical value if the manufacturing companies in a responsible way collect clinical information of all patients with regard to efficacy and safety. Such information should advance the field of biosimilars even if those biocopies do not meet the standard of approval in EU or USA.

**each biopharmaceutical is a unique product**

Biopharmaceuticals are large recombinant proteins, e.g. hematopoietic growth factors, 15–20 kDa, and monoclonal antibodies, 150 kDa, in comparison to most chemical cytotoxic agents which are <1 kDa. The complexity of biological products is determined by the product itself as well as by the production and handling procedures (Table 1).
Biopharmaceuticals are produced by living cells and undergo complex post-translational modifications. In the field of biotechnology products, it is said that 'the process is the product'. Even knowing the DNA-coding sequence, it is very difficult to replicate its precise end structure (e.g. tertiary and quaternary structures), including glycosylation, methylation, etc., as well as to replicate the manufacturing process. The manufacturing protocols are proprietary knowledge of the originator pharmaceutical company. The manufactures of biosimilars cannot exactly duplicate the production process of the reference product [6, 7].

In the comparability exercise [1, 2, 8] of a biosimilar product submitted to the regulatory authority in the application dossier, a lot of advanced biochemical analytical methods are used to characterize the product, e.g. composition and primary structure, higher-order structure conformation, post-translational modifications, polarity, charge, isoforms, size, detection of aggregates, binding and biological activity. If the comparability exercise shows significant biophysical and biochemical variations compared with the reference product, the application will be rejected but non-significant variations should be allowed taking into account the complexity of biopharmaceuticals. However, the present analytical tools do not allow the detection of differences, e.g. in folding and post-translational modifications, which might have consequences for bioactivity and immunogenicity [6, 7].

The EMA ‘Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues’ was adopted by CHMP (Committee for Medicinal Products for Human Use) 30 May 2012 and came into effect on 1 December 2012 [8]. This guideline is much more extensive than the guidelines for hematopoietic growth factors partly depending on the higher complexity of monoclonal antibodies when compared with growth factors, but also due to the experiences that have been acquired during the past years.

Step-wise non-clinical in vitro and in vivo approaches are described to evaluate the similarity of the biosimilar and the reference monoclonal antibodies to assure non-significant variations of the product according to the best available tools. Clinical PK studies have to be accomplished to proof similar PK profile preceding clinical efficacy trials. PK is inevitably highly variable even within a clinical indication, e.g. adjuvant or metastatic breast cancer. It may be necessary to explore PKs as part of the clinical study to establish similar clinical efficacy.

Pharmacodynamic parameters are also contributing to the comparability exercise. For erythropoietin and filgrastim, there are excellent pharmacodynamic markers as hemoglobin concentration/reticulocyte counts and absolute neutrophil counts, respectively, but for anti-neoplastic antibodies there have been so far no pharmacodynamic markers for an antitumor response, which may hamper a rational clinical efficacy comparability exercise.

EMA underlines the challenge to establish a similar clinical efficacy and safety of biosimilar and the reference monoclonal antibody. A specific section is included on ‘Additional consideration for mAbs license in anticancer indications’ in the guideline [8]. 'According to the “Guideline on the evaluation of anticancer medicinal products in man” (CHMP/EWP/205/95)

---

**Figure 2.** Expire dates for some biopharmaceuticals in oncology in EU (ϕ) and United States (ϕ).

**Table 1.** Biopharmaceuticals are complex products

<table>
<thead>
<tr>
<th>Inherent complexity</th>
<th>Added complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Manufactured process</td>
</tr>
<tr>
<td>Structure</td>
<td>Host cell</td>
</tr>
<tr>
<td>Primary (amino acid sequence)</td>
<td>Cell bank</td>
</tr>
<tr>
<td>Secondary (α/β sheets)</td>
<td>Protein production</td>
</tr>
<tr>
<td>Tertiary (folding)</td>
<td>Protein purification</td>
</tr>
<tr>
<td>Quaternary (polypeptide arrangements)</td>
<td>Analytical methods</td>
</tr>
<tr>
<td>Physicochemistry</td>
<td>Formulations</td>
</tr>
<tr>
<td>(glycosylation and methylation)</td>
<td>Storage and handling</td>
</tr>
<tr>
<td>Heterogeneity (isoforms)</td>
<td></td>
</tr>
</tbody>
</table>

Biopharmaceuticals are produced by living cells and undergo complex post-translational modifications. In the field of biotechnology products, it is said that ‘the process is the product’. Even knowing the DNA-coding sequence, it is very difficult to replicate its precise end structure (e.g. tertiary and quaternary structures), including glycosylation, methylation, etc., as well as to replicate the manufacturing process. The manufacturing protocols are proprietary knowledge of the originator pharmaceutical company. The manufactures of biosimilars cannot exactly duplicate the production process of the reference product [6, 7]. In the comparability exercise [1, 2, 8] of a biosimilar product submitted to the regulatory authority in the application dossier, a lot of advanced biochemical analytical methods are used to characterize the product, e.g. composition and primary structure, higher-order structure conformation, post-translational modifications, polarity, charge, isoforms, size, detection of aggregates, binding and biological activity. If the comparability exercise shows significant biophysical and biochemical variations compared with the reference product, the application will be rejected but non-significant variations should be allowed taking into account the complexity of biopharmaceuticals. However, the present analytical tools do not allow the detection of differences, e.g. in folding and post-translational modifications, which might have consequences for bioactivity and immunogenicity [6, 7].

The EMA ‘Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues’ was adopted by CHMP (Committee for Medicinal Products for Human Use) 30 May 2012 and came into effect on 1 December 2012 [8]. This guideline is much more extensive than the guidelines for hematopoietic growth factors partly depending on the higher complexity of monoclonal antibodies when compared with growth factors, but also due to the experiences that have been acquired during the past years.

Step-wise non-clinical in vitro and in vivo approaches are described to evaluate the similarity of the biosimilar and the reference monoclonal antibodies to assure non-significant variations of the product according to the best available tools. Clinical PK studies have to be accomplished to proof similar PK profile preceding clinical efficacy trials. PK is inevitably highly variable even within a clinical indication, e.g. adjuvant or metastatic breast cancer. It may be necessary to explore PKs as part of the clinical study to establish similar clinical efficacy.

Pharmacodynamic parameters are also contributing to the comparability exercise. For erythropoietin and filgrastim, there are excellent pharmacodynamic markers as hemoglobin concentration/reticulocyte counts and absolute neutrophil counts, respectively, but for anti-neoplastic antibodies there have been so far no pharmacodynamic markers for an antitumor response, which may hamper a rational clinical efficacy comparability exercise.

EMA underlines the challenge to establish a similar clinical efficacy and safety of biosimilar and the reference monoclonal antibody. A specific section is included on ‘Additional consideration for mAbs license in anticancer indications’ in the guideline [8]. 'According to the “Guideline on the evaluation of anticancer medicinal products in man” (CHMP/EWP/205/95)
the preferred end point to prove efficacy in cancer indications would be either progression free (PFS), disease free (DFS) or overall (OS) survival. Such endpoints are important to establish patient benefit for a new anticancer drug, but may not be feasible or sensitive enough for establishing comparability of a biosimilar monoclonal antibody to a reference mAb since they may be influenced by various factors not attributable to differences between the biosimilar monoclonal antibody and the reference monoclonal antibody, but by factors like tumor burden, performance status, previous treatment etc and may therefore not be suitable for establishing similar efficacy of the biosimilar and the reference monoclonal antibody according to EMA.

The focus of the comparability exercise according to EMA is to demonstrate similar efficacy and safety compared to the reference monoclonal antibody and not a patient benefit per se which has already been established by the reference medicinal product. The most sensitive patient population and the clinical end-point is preferred to be able to detect product-related differences, if present, and at the same time to reduce patient and disease-related factors to a minimum to increase precision. A clinical trial in a homogeneous patient population with a clinical end-point that measures activity as primary end-point maybe considered. EMA indicates ORR and ORR at certain time points or percentage of change in tumor mass from baseline or pathological complete response. PFS and OS should be recorded. In case PFS is likely to be more sensitive than ORR as an outcome measure, this is the preferred option even though this will prolong the clinical study.

Novel end points may be tested on an exploratory basis and may add supportive evidence for biosimilarity.

The italic text is a summary of the EMA Guidelines for clinical efficacy of monoclonal antibodies which is of importance to understand the basis for the approval process by EMA.

There is a lively debate ongoing among clinicians whether the ORR is an acceptable clinical end point in the clinical efficacy comparability exercise. The clinical end point should be discussed point by point to obtain wide acceptance among oncologists. A major concern among clinicians is that anti-neoplastic monoclonal antibodies are used to treat patients with a curative intent, and such patients should not be exposed to a treatment option where the therapeutic efficacy is not fully clinically established. Clinicians do not want to put patients into risk although the comparability exercise has shown ‘non-significant’ variations compared with the reference monoclonal antibodies, but still there might be differences that may not be detected until a larger patient population has been treated and followed for a long time.

Rituximab in combination with chemotherapy is a standard treatment for diffuse large B-cell lymphoma (DLBCL) and a potential curative treatment with 75% complete responses and 5 and 10 years PFS of 50% and 30%, respectively [9]. However, response rates in DLBCL may not necessarily relate to PFS and OS [10]. In advanced indolent and low-grade follicular lymphoma, also a fraction of patients might be cured but at least 8 years follow-up might be necessary [11]. Thus, in lymphomas, ORR alone might not be an adequate end point for measurement of clinical activity, but a long-term follow-up is needed (at least 5 years).

In an abstract report from India of a retrospective non-randomized study of DLBCL patients, 101 patients were treated with the innovator rituximab and 72 with a biosimilar rituximab. In this very preliminary study, there were no statistically significant differences in ORR, PFS and OS comparing the two treatment groups [12]. Prospective, randomized studies including long-term follow-up are mandatory.

Furthermore, as extrapolation according to the regulation might be allowed, clinicians feel uncomfortable to extrapolate data from follicular lymphoma to DLBCL based on the ORR only.

Rituximab is also used to treat inflammatory disorders such as rheumatoid arthritis, ankylosing spondylitis, psoriasis and Crohn’s disease. As extrapolation is allowed, the results from a rheumatoid arthritis trial using rituximab may technically be extrapolated to cancer diagnosis, but this has been indicated by EMA not to be the case.

Similar arguments for rituximab could also be applied for a biosimilar trastuzumab in breast cancer. Is it sufficient to study trastuzumab in combination with chemotherapy in metastatic breast cancer and only report on ORR? Could clinical efficacy results from metastatic breast cancer be extrapolated without testing the adjuvant clinical setting of breast cancer or should a separate trial be carried out with at least 5 years follow-up? These questions have to be addressed and professional medical societies should be involved.

**immunogenicity**

Antibodies against rituximab are rarely seen in rituximab-treated patients with B-cell malignancies but more frequently in auto-immune disorders (M.Wadhwa personal communication). Of special interest are those antibodies recognizing the idiotype, i.e. binding to the antigen-binding region of the therapeutic monoclonal antibody and thereby, have the capability to inhibit the effect of the therapeutic antibody. Such anti-idiotypic antibodies have been noted in C.LL patients treated with subcutaneous administration of alemtuzumab [13]. As monoclonal antibodies, biosimilars may exhibit small differences in the molecular structure compared with the innovator antibody, which may alter the immunogenicity profile, formation of antibodies against the biosimilars should be carefully analyzed to exclude that reduced efficacy might not be due to induction of antibodies as has been shown for infliximab in rheumatoid arthritis patients [14]. At the time of registration, there is limited information on immunogenicity against the biosimilar antibody. A detailed careful risk management and pharmocovigilance plan for the biosimilar monoclonal antibody is important to accomplish and fully characterize clinical and safety concerns for a biosimilar anti-neoplastic monoclonal antibody.

**interchangeability and substitution**

Interchangeability means that the same biopharmaceutical products are fully interchangeable for each other based on a scientific process without a loss of efficacy and increase in safety. To be considered interchangeable, the safety and efficacy risk of a biosimilar monoclonal antibody must not be greater than the risk
of using the reference monoclonal antibody without switching. EMA has refrained from recommendations on interchangeability which is at the decision by the national authority.

Automatic substitution is a legal process where the pharmacists are allowed to substitute drugs for each other based on the national regulation.

Interchangeability will probably not be allowed until the biosimilar has an extensive track record and is shown through postmarketing studies to produce results identical to that of the reference product. It has also been discussed for interchangeability to carry out cross-over studies but such studies would be too expensive and unrealistic to carry through.

An interesting document was produced in 2011 by the Swedish Medical Product Agency (MPA) for ‘Requirements for extended substitution and substitution at first treatment’ [15] which is also applicable for interchangeability. ‘MPA considers that the drugs (biopharmaceutical innovator as well as biosimilar products) cannot be regarded as medical comparable and do not admit substitution. There might be differences in immune responses for patients at the use of biopharmaceuticals. It is unclear which immunological reactions at substitution of these products may be induced. Furthermore, these drugs are injectable and delivered by administration devices and because of that not suitable for substitution. Moreover, approval of biosimilars is linked to risk management plans, which include safety pharmacovigilance, which should be difficult to accomplish if substitution is done at the pharmacy’. It seems to be clear that biosimilars and innovator biopharmaceuticals are not interchangeable, underlining that these drugs are to some extent different.

**switching**

Switching in this context means that patients during the treatment period can receive the same type of biopharmaceutical made by different manufacturers. Theoretically, as the different products are not the same there might be a higher risk for immune-related side-effects. This matter is still an open question, but at present the same drug is recommended to be administered to a patient throughout the treatment period irrespectively of whether it is an innovator drug or a biosimilar. At present, there are, however, no scientific data supporting or rejecting such an approach. In a register study, there seems to be no risk for increased side-effects by switching of erythropoietins [16].

**Economical aspects**

The main purpose of producing biosimilars are to reduce the costs of drugs. Improved drugs is not an issue as these will be ‘bio-betters’ and not applicable for the biosimilar regulatory pathway.

The global spending for biological and biosimilars in the period of 2011–2015 is estimated to be US $200 billions of which costs only 1% are biosimilars [17]. However, during this time period the great block-busters as infliximab, adalimumab, rituximab, cetuximab, trastuzumab and bevacizumab still have patent protection. After that time period, biosimilar monoclonal antibodies will enter the market and change the relationship. The costs of biosimilars in percent of costs of biologicals in advanced economies as Japan, EU and Canada is low, (<5%) at the present, while in emerging markets as China, Brazil, India, Korea and Mexico 20%–60% of the costs for biologicals are biosimilars [18]. However, in the pharmaemerging markets loos approval apply for products that resemble biosimilars.

The price reduction in Europe for biosimilars is estimated to be 20%–30% of the innovator drugs but a market price competition will be seen which will also reduce the price for the innovator drugs. In some countries, a market price reduction (30–40%) for innovator filgrastim and erythropoietin has already been noted. However, the cost of drugs for cancer healthcare is only part of the total healthcare costs for cancer (10%–15%), which should be kept in mind when evaluating the risk–benefit ratio for biosimilar therapy.

**Conclusions**

Biosimilar anti-neoplastic monoclonal antibodies are entering the market and will play a role in the future therapeutic arsenal. At the time of approval, limited information is available on clinical safety and efficacy. It is therefore of importance, with a careful pharmacovigilance plan and rapid dissemination of information on biosimilars, to increase the acceptance of biosimilars. Oncologists should be aware of the concept of biosimilars to be able to actively contribute to a sound scientific and clinical introduction of

Table 2. Pros and cons of biosimilar anti-neoplastic monoclonal antibodies

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural characterization and manufacture well established</td>
<td>Every monoclonal antibody is unique and small structural changes may have clinical consequences</td>
</tr>
<tr>
<td>Available potency assays</td>
<td>Assays might not be able to discriminate the differences in clinical significance</td>
</tr>
<tr>
<td>Function well established</td>
<td>Functions, species specific, which make preclinical in vivo studies not valid</td>
</tr>
<tr>
<td>Efficacy and safety established for tested indications</td>
<td>Efficacy and safety tested in a limited patient group might not be extrapolated</td>
</tr>
<tr>
<td>Substitution may be allowed depending on the legal aspects providing no switching and traceability preserved</td>
<td>Immunogenicity profile not well established</td>
</tr>
<tr>
<td>Fulfill an unmet economic need</td>
<td>Interchangeability may not be allowed</td>
</tr>
<tr>
<td></td>
<td>A 20%–30% decrease in cost at the end might not be sufficient to justify the whole biosimilar effort</td>
</tr>
</tbody>
</table>
biosimilars for the best of the patients. In Table 2 pros and cons of anti-neoplastic biosimilar antibodies are shown.

**disclosure**

The author has declared no conflicts of interest.

**references**


