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# From the Biosimilar Concept to the Marketing Authorisation

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## Introduction

The concept of similar biological medicinal products similar to a reference biological medicinal product has been recently introduced in the European legislative framework. As it has been stated in this book's introduction, the biosimilar term designates in common language the "copy" concept of a biological medicinal product. The purpose was to open a regulatory route for pharmaceutical companies willing to develop biosimilar medicinal products once the marketing protection of the "reference" biological medicinal product expired.

Several medicines of this particular field are or will have expired patents in the near future, which offers pharmaceutical companies the possibility to develop similar products and to obtain the same therapeutic indications as the reference products.

Even if this strategy could be easily assimilated to the standard generic approach (which, for a chemically derived substance, requires a single demonstration of bio-equivalence with the reference product), the generic approach was not considered adequate to establish the quality, safety, and efficacy of biosimilars. That is due to the

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complexity of the biotechnology-derived products themselves as well as their manufacturing process. In most cases, molecular complexity and heterogeneity inherent to biological products do not allow for their full and guaranteed characterization.

The quality attributes of the active ingredient are highly dependent on its manufacturing process and any change in the manufacturing process may affect the quality attributes and impact on the safety or efficacy profiles of the product. Therefore the European legislation has provided a specific regulatory framework (called “biosimilar approach”) for biological medicinal products similar to reference biological medicinal products. It is applicable to any biological medicinal product, which confers an originality to the European regulation and its unique character. Practically, the biosimilar approach developed in the recommendations for approval application apply to well-characterized recombinant proteins, such as insulin, somatropin, erythropoietin, G-CSF (Granulocyte Colony Stimulating Factor). Other recommendations have been issued for low molecular weight heparins and alpha interferon, or are being drafted for monoclonal antibodies. These guidelines are made by the CHMP (*Committee for Medicinal Products for Human Use*) of the European Medicines Agency (EMA); they are relevant to quality, non-clinical and clinical issues to be developed in order to be addressed for a biosimilar approval application.

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## Definition of Biosimilars

“When a biological medicinal product similar to a reference medicinal product does not meet the conditions stated in the generics definition, notably because of differences linked to raw material or differences between manufacturing processes of the product and the reference product, appropriate preclinical or clinical studies related to these conditions must be provided.” [European guideline 2004/27 art.10 (4)].

In this chapter the general recommendations will be summarized and analysed in relation to the development quality of a biosimilar, followed by those related to preclinical tests necessary before the first human administration. The general recommendations for a clinical evidencing of similarity in terms of safety and efficacy will be particularly developed for biosimilars used in oncology and haematology. These essentially concern erythropoietin and the growth factor G-CS for which the first biosimilars have been put on the market.

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## Pharmaceutical Authorisation Background

General recommendations appear in a general text on biosimilars, which introduces the concept of biosimilarity and gives a definition of the main principles of biosimilars development in terms of quality, safety and efficacy.<sup>1</sup> A company

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<sup>1</sup> Guideline on Similar Biological Medicinal Products. CHMP/437/04 (CHMP adopted September 2005).

developing a medicinal product similar to a reference biological medicinal product must choose the reference among medicines authorized by a complete file with the European Community. The concept of a biosimilar is applicable to any biological medicinal product. However, in practice, demonstrating the similarity will depend on a possible complete characterisation of the product. For that it is necessary to have not only data on physico-chemical and biological properties, but also to know the manufacturing process and its controls. As minor changes in this manufacturing process may alter the product at a molecular level, the biological product safety and efficacy profile depends on the robustness and follow-up of quality issues.

The biosimilar approach takes into account the following points:

- the “standard” generic approach is not considered as acceptable. The biosimilar approach is based on exercises of comparability due to the complexity of biotechnology-derived products;
- exercises of comparability can only apply to highly purified products that may be correctly characterized. It is not always the case, notably for extraction products with biological sources, or those for which only a limited clinical and regulatory experience is available;
- the biosimilar approach is defined by the current recommendations on analytical methods, manufacturing process, and clinical studies conducted for the approval application;
- by definition, a biosimilar product is not a generic product; subtle differences between biosimilar and reference may exist and call for a prior experience before using them. In order to facilitate a later follow-up (pharmacovigilance), patients receiving a biosimilar must be clearly identified.

In the same general recommendations, the same biological reference must be used for the whole program of comparability of quality safety and efficacy studies, in order to ensure that responses during the comparability exercise be obtained with a single comparator, having all along the studies concerning the same form and same dosage, the same types of impurities and variants linked to its manufacturing process. A biosimilar’s active substance must be similar in molecular and biological terms to the reference product. For instance an  $\alpha$  2a-interferon cannot be biosimilar to an  $\alpha$  2b-interferon. It is strongly recommended for the biosimilar medicinal product to have the same form, dosage and route of administration as the reference medicinal product. If it is not the case, additional data must be given in the context of comparability exercise to justify these differences. Any difference between biosimilar and reference must be justified by appropriate study, case by case. A consultation with regulatory authorities is recommended for discussing these approaches.

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## Quality Control Approach

Biosimilars are biological products developed according to their own manufacturing process. Scientific data coming from pharmacopeia’ monographs or published in the literature on the reference biological medicinal product are considered as limited in order to establish the similarity between biosimilar and

reference at the active substance and finished product levels, for they are not relevant enough. Only a comparability exercise will allow the evaluation of similarity in terms of quality, safety and efficacy. Based on a complete quality dossier combined with sensitive analytic tests, the comparability exercise at the quality level allows the reduction of the number of non-clinical and clinical studies, compared to a complete approval application file.

A complete quality file, comparable to the file required for the reference medicinal product approval, is always required for biosimilars approval applications. It is completed with quality, non-clinical and clinical comparability data between the reference medicine and the biosimilar medicine.

## **Biosimilars' Manufacturing Process**

The biosimilar is defined by its manufacturing process specific to the active substance and to the finished product (as for the reference medicinal product). These processes must be developed and optimized according to current regulatory recommendations, covering aspects of the molecular expression system and of the production cells, culture, purification, viral protection, formulation excipients, interactions with primary packaging materials, as well as their possible consequences upon the finished product characteristics. Besides, every medicine is defined by its molecular composition, which is itself defined by its manufacturing process which introduces its own impurities. For these reasons, the biosimilar is defined by:

- the molecule itself, including variant products and impurities;
- the manufacturing process which may play upon molecular characteristics and impurities.

The company that develops the biosimilar must master all these issues in terms of reproducibility and robustness of the processes involved. It is recommended that clinical data in the comparability exercise be obtained with the biosimilar manufactured according to the final manufacturing process that will be used for batches to be marketed. Otherwise “bridge” studies will be needed.

## **Quality Comparability Exercise**

Quality issues are essential for a biosimilar and their potential impact on safety and efficacy must always be evaluated. A step by step approach is recommended in order to analyse and justify any difference in the quality attributes between biosimilar and reference. It is not demanded that the quality attributes be identical as minor structural differences may exist for the active substance, due to the post-translational modifications' variability or differences in impurities profile.

These may be acceptable but must be justified, notably in terms of their possible impact upon safety and efficacy of the finished product.

## Analytical Methods

Characterisation studies must be conducted according to regulatory current recommendations concerning the active substance and at the same time the final product to demonstrate that the biosimilar quality is comparable to that of the reference. The analytical methods must be chosen according to the product's complexity and must be able to detect differences between biosimilar and reference. The comparison is done with validated analytical methods assessing composition, physical properties, primary and higher degree's molecular structure, different forms related to post-translational modifications, and biological activities. Several biological tests are needed; they use various approaches in order to compare the biosimilar's and reference's biological activity. Activity expression must be stated in international units, if an international standard exists.

A biosimilar's derived products and impurities must be identified and compared to its reference's using current available techniques. Stress studies are used to show specific degradations (*i.e.* oxidation, dimerization) and accelerated stability studies lead to profiles of stability that can be compared between biosimilar and reference.

Impurities related to the manufacturing process (proteins and DNA [deoxyribonucleic acid] of the host cell, reagents, purification impurities) are specific and depend on the manufacturing process of each product. Because of this the comparability exercise may not be applied in an absolute manner. However the biosimilar, as the reference product, must meet the same level of requirements described in the recommendations on biotechnology-derived products quality.

## Specifications

As with any biotechnology-derived product, the specifications are based on a selection of tests depending on the given product. The rationale for fixing the limits of acceptance criteria must be described and developed following the same approach as for any biological medicinal product. Each acceptance criterion must be established and its justification must be based on batches used in non-clinical and clinical studies, on batches produced in a reproducible way, and on data coming from comparability exercise (quality, safety, efficacy).

To fix specifications, the company that files the marketing authorisation application must use a global reasoning: this application is based on experience acquired from the product being developed and its reference medicine. Data must

show, if possible, that the limits of a given test are not wider than the variability deviations observed with the reference medicinal product.

## Conclusion on Quality

The quality aspect in a biosimilar's development is essential. It is on that aspect that mostly lays the demonstration of similarity between biosimilar and reference. The quality file of a biosimilar must contain the two following demonstrations:

- characterisation and production full studies, on active substance and on finished product;
- a comparability exercise to evaluate the quality and similarity of the biosimilar and the reference. These studies have to be interpreted in the context of safety and efficacy comparable between biosimilar and reference. In the biosimilar approach, if data concerning quality are crucial, they have, however, to be completed with data coming from non-clinical and clinical comparative studies, more limited than those required for the development of a brand new medicine.

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## Non Clinical and Clinical Aspects

Quality, safety and efficacy are key issues that must be followed during a medicine's whole life. For a typical chemical medicine, pharmaceutical development is well-defined. It includes data to document the pharmaceutical quality and is completed by preclinical, called toxicological data, before the first human administration. Clinical development requires data concerning a proof of concept, dose evaluation and demonstration of efficacy in pivotal studies conducted in the medicine's target population. Based on quality, preclinical and clinical studies, stored during its development, the medicine may be ready to be filed in order to get a Marketing Authorisation (MA). As for chemical medicines, the application biosimilar approach necessitates the development of the manufacturing process (for the active substance and finished product), and the demonstration of safety and efficacy through non-clinical and clinical studies. However, as the reference biological medicinal product has been already approved and used for many years in the European Union, its data are available in the public domain. Consequently, a biosimilar development calls for less non-clinical and clinical data than a new medicine; some of this data may be taken as given with the reference product and be used as "support" data in the biosimilar file. Thus, if the reference is approved in several clinical indications, and its mechanism of action is the same in all approved indications, then it is possible to assume that there is a "therapeutic similarity" between reference and biosimilar and to extrapolate the biosimilar efficacy demonstrated for one indication to other indications of the reference medicinal product.

## Preclinical Approach

Preclinical studies are comparative and generally include in vitro studies of receptor bindings and tests on cells already found in quality data provided for the biological activity evaluation. These studies can establish the comparability in terms of their mechanism of action between compared products and identify causality factors in case comparability could not be established. In vivo studies on relevant animal studies must be added, while taking into account the regulatory guidelines in force.

Preclinical study has to evaluate, when the animal model allows it:

- activity in connection with the pharmacodynamic effect relevant to the clinical application;
- non-clinical toxicity determined with a single and repeated dose; it is not necessary to have toxic dose finding studies, as they are already known. Measurements in toxicokinetics include the determination of the level of antibodies with the study of crossed reactions and of the neutralisation capacity; the studies must last long enough to show any difference relevant in terms of toxicity and/or immune response between the biosimilar and the reference product;
- if necessary, local tolerance comparative studies.

Other routine toxicological tests (safety pharmacology, reproductive tests, mutagenicity, carcinogenicity) are not necessary. The preclinical studies program is a limited program due to the fact that the toxicology data are known for the reference medicinal product and it is not necessary to repeat all the studies to know the biosimilar.

## Clinical Approach

The exercise of clinical compatibility is done step by step; it generally starts with pharmacokinetics and pharmacodynamics studies in healthy volunteers. These studies are followed by efficacy and safety comparative studies. In most cases, the clinical efficacy studies are conducted to demonstrate a therapeutic equivalence between the biosimilar and the reference in a population of patients chosen for the most sensitive to the studied medicinal product effects in order to evidence any difference that could be exist between biosimilar and reference. However, even if efficacy is demonstrated through a therapeutic equivalence test, a biosimilar tolerance may differ from the reference's if there are differences in terms of quality attributes not apparent or difficult to analytically demonstrate. These differences may have unpredictable clinical consequences, and a biosimilar clinical tolerance must be continuously evaluated before and after its marketing authorisation.

During the evaluation of clinical tolerance, a special attention has to be paid to immunogenicity, because patients may develop against the biosimilar as against any recombinant protein in some circumstances; these antibodies could have

clinical consequences. The immunogenic potential of a biological medicinal product differs between products and depends on several factors like the active substance's nature and structure, impurities, excipients of the medicine, manufacturing process, route of administration, and target population. These differences may compromise the product in vivo behaviour, with, as a consequence, undesirable effects for the host that may minimize the intended clinical effect with potentially lethal reactions.

Different approaches based, for instance, upon the response of the epitope to Human Leucocyte Antigen (HLA) polymorphism, or the immunological response studied in relevant animal models, may be used to evaluate a biosimilar immunological profile. However, if these responses are important to identify the antigenic profile, they are not predictive of the immunological response to the biosimilar in vivo. Evaluation of a biosimilar antigenic profile in patients is complex because of the difficult measurement of antibodies' level (unavailability of immune serums, absence of appropriate standards, interference of endogenous proteins, limits of analytical methods, etc.) Similarly, the simple comparison of products of the same therapeutic class, although interesting on a theoretical level, is not enough and may be the source of misinterpretation.

Overall, the decision to put a biosimilar on the market is made if its efficacy is similar and its immunogenic profile is at least comparable or improved in comparison to the reference product. However, this decision is made on limited data. The comparability program may disclose substantial differences in terms of immunogenic profiles but is probably unable to detect minor differences and rare events. For that, clinical trials complemented by a pharmacovigilance program are essential for evaluating a recombinant protein's safety in patients. Some undesirable effects are very rare and require a follow-up during the medicinal product's whole life; this is particularly true for biosimilars.

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## Recommendations in Onco-Haematology

### Hematopoietic Growth Factor (rG-CSF)

The file of a biosimilar of Recombinant Granulocyte Colony-Stimulating Factor (rG-CSF) that positions itself as similar to a medicine already approved in the European Community and whose patent has expired must demonstrate its comparability in terms of non-clinical and clinical quality with the reference product.

The human G-CSF is a protein made of 174 amino acids with an O-glycosylation site on a threonine. The recombinant protein obtained in *E.coli* is not glycosylated and presents an additional terminal methionine. The rG-CSF protein has a free cysteine and two disulfide bonds. The medicines rG-CSF obtained by expression in *E. coli* (*Filgrastim*<sup>®</sup>) and in CHO [Chinese Hamster Ovary] (*Lenograstim*<sup>®</sup>) are clinically used for several indications:



- reduction of the duration of a severe neutropenia after a cancer chemotherapy or myelosuppressive treatment followed by a bone marrow transplant;
- mobilisation of hematopoietic stem cells in peripheral blood (Peripheral Blood Progenitor Cell [PBPC]);
- treatment of severe congenital, cyclic or idiopathic neutropenia
- treatment of persistent neutropenia in Human Immunodeficiency Virus (HIV) patients.

### **Doses Vary with Indications**

G-CSF acts on target-cells through a membrane receptor. Only one soluble isoform that attaches itself to the extracellular part of the receptor is known. The extracellular binding domains of known isoforms are identical. Consequently, G-CSF effects are mediated by only one class of receptors.

The approval application and marketing of a G-CSF biosimilar require comparative studies of non-clinical and clinical quality.

### **Non Clinical Program for rG-CSF**

The non-clinical program includes:

- comparative pharmacodynamic studies:
  - in vitro at receptor level on adapted cellular models, to measure biological activity;
  - in vivo on neutropenic and non neutropenic rodent models, in order to compare the biosimilar effects to those of the reference;
- toxicology studies with a single or repeat dose to a relevant species for at least 28 days.

Other routine toxicity tests are not required.

### **Clinical Program for rG-CSF**

The clinical program to compare biosimilar to the reference product includes:

- pharmacokinetics studies in crossed single dose for the different routes of administration (subcutaneous, and intravenous) in healthy volunteers. Studied parameters include the area under the curve (AUC), the C max and T  $\frac{1}{2}$  with an evaluation performed according to bioequivalence general principles;
- pharmacodynamics studies—the absolute number of neutrophils is the pharmacodynamics marker the most relevant for G-CSF activity. The pharmacodynamics study may be done during the pharmacokinetics with a dose selection in the ascending linear part of the dose–response curve; repeat dose studies may be necessary. CD34+ level is a secondary pharmacodynamic parameter;
- the clinical model suggested for efficacy clinical studies is the prophylaxis of severe neutropenia after cytotoxic chemotherapy in a group of patients homogenous in terms of tumour type and in terms of programmed and validated chemotherapies according to the tumour stage. A two-arm study comparing

biosimilar and reference is recommended with the measurement of frequency and duration of neutropenia as the efficacy main criterion. The company must justify the clinically acceptable difference in the severe neutropenia duration ( $ANC < 0,5 \times 10/L$ ) between the biosimilar and the reference. This evaluation will be done during the first cycle of chemotherapy;

- G-CFS effects are mediated by only one class receptors and the results of clinical comparability obtained on the model may be extended to other indications of the reference product;
- clinical safety must be evaluated from a cohort of patients who have received repeat doses of biosimilar, preferably during the comparative phase of the clinical trial. The total exposure of patients must correspond to the normal exposure of the conventional treatment with a corresponding number of chemotherapy cycles. The duration of the study must not be shorter than six months and must integrate immunogenicity data. The number of patients must be sufficient for evaluating the secondary effects including bone pains and biological parameters;
- a strengthened program of pharmacovigilance must be implemented with a risk management plan. The two must take into account that immunogenic events are rare but serious in patients with a chronic administration.

## Erythropoietin

Human erythropoietin (EPO) is a 165 amino acid-glycoprotein produced in the kidney, that stimulates the production of red blood cells. The medicine is obtained from recombinant DNA technology in mammal cells able to express a glycosylated protein.

The recombinant protein has the same sequence as the natural protein but differs by the number and types of isoforms. The protein's glycosylation influences efficacy and safety including the protein's immunogenicity.

Erythropoietin based medicines are indicated in various conditions such as anemia in patients suffering from chronic renal insufficiency in patients treated by a cancer chemotherapy inducing an anemia, and also in some programs of autologous transfusions differed in order to increase the number of autologous blood donations. The active substance's mechanism of action is the same for all indications currently approved but the doses to get the desired response vary a lot and are generally higher for cancer indications. The medicine is injected by IV or SCD.

As it is generally well-tolerated, EPO allows a range of therapeutic concentration relatively wide. The hemoglobin content reached allows a control of the bone marrow stimulation and consequently of doses and periodicity of the treatment. The hemoglobin content increase varies considerably between patients and depends on numerous factors like dose and administration rhythm but also the level of iron in the body, basal content of hemoglobin and endogenous erythropoietin, and concomitant treatments or patient's underlying condition, such as inflammation.

The pharmacodynamic response must be under control to avoid serious undesirable effects like high blood pressure and thrombotic complications. Cases of Pure Red Cell Aplasia resulting from the production of anti-erythropoietin neutralising antibodies have been observed, mainly in patients with chronic renal insufficiency and treated with sc injections. Stemming from the fact that usually these antibodies' production is a very rare event, clinical studies for pre-marketing authorisation do not identify these events. Other considerations have to be taken into account for erythropoietin approval applications that are their possible angiogenic action and tumour promoter. Thus the study population selection is particularly important.

The approval application files for a new biosimilar erythropoietin involve the demonstration of comparability with the reference product in terms of quality, safety and efficacy.

### **Non Clinical Program for EPO**

The non-clinical studies include:

- pharmacodynamic comparative studies:
  - in vitro to evaluate the absence of altered response on receptors, with tests of binding to receptors or with cellular proliferation tests. Some tests come from quality comparative studies;
  - in vivo to evaluate the erythrogenic action on relevant animal models. Information on the erythrogenic activity may be obtained through toxicity studies with repeat doses or specifically with a methodology like the one described in on mice in the European Pharmacopeia (Normocythaemic Mouse Assay);
- single and repeated dose toxicity studies on a species relevant to rats. The studies must last at least four weeks and include a toxicokinetics evaluation;
- local tolerance studies, notably with repeated doses with subcutaneous injections.

Other routine toxicity tests are not required.

### **Clinical Program for EPO**

The clinical program is comparative between copy and reference; it is made of pharmacokinetics studies in crossed single dose for the different routes of administration (subcutaneous, and intravenous) in healthy volunteers. The dose has to be chosen in the sensitive part of the dose–response curve. Studied parameters include the area under the curve (AUC), the C max and T  $\frac{1}{2}$ . The bio-equivalence margins must be beforehand defined and justified;

- the pharmacodynamic parameters must be preferably studied during pharmacokinetics. In single dose studies, the most relevant parameter is the number of reticulocytes, for it is a pharmacodynamic marker of erythropoietin's activity. However this marker does not substitute for efficacy, since it is not directly correlated with hemoglobin level;
- clinical biosimilarity must be demonstrated by comparative clinical studies powerful enough, randomised and in parallel groups between biosimilar and

reference. As pharmacokinetics and efficient doses differ between IV and SC routes, studies must be conducted on each mode of injection. The studies may be conducted either separately for each route, or for one route with appropriate “bridge” data for the other route. Double blind studies are preferable in order to avoid any bias;

- sensitivity to erythropoietin is better for patients who have a deficit in endogenous erythropoietin than for patients without a deficit. Patients with chronic renal insufficiency without major complications will be preferred as a model population for the biosimilar’s clinical trials. The other possible anemia causes will be excluded from the comparability studies. The populations in dialysis and pre-dialysis shall not be mixed, as the doses needed to maintain the hemoglobin level are not the same;
- it is possible to demonstrate efficacy’s similarity through different options and recommendations. Two different clinical trials are conducted; the trials may combine a phase of anemia correction by sc injections (for instance for a pre-dialysis population) and a maintenance phase by iv injections (for instance for an haemodialysis population). During the correction phase, the dynamic response and the dose may be determined by carefully checking on the safety profile of biosimilar’s patients. This phase may include treatment-na patients or patients already on treatment after a three-month treatment free period. In the maintenance phase, patients must have an optimal titration on reference product for at least 3 months. After this period, they are randomised between biosimilar and reference product, while keeping the erythropoietin prerandomisation dose, as well as the periodicity and the administration route. For the correction phase, the responder rate or the change in hemoglobin level may be chosen as a primary endpoint of clinical activity. Anyway, dosing erythropoietin remains the trial’s secondary endpoint. A four-week evaluation period is necessary for a study lasting 5–6 months, for the correction phase as well as for the maintenance phase. The studied must be designed according to a methodology fit for evaluating the equivalence between the two products; another approach is to conduct a comparative efficacy study for one route of administration and to provide, for the other route, data resulting from “bridge” studies comparative of PK/PD in single dose and multiple dose, conducted in a population sensitive to erythropoietin (for instance healthy volunteers). The PK/PD study in multiple doses must last four weeks minimum, with a fixed dose of EPO with a primary endpoint fixed on the evolution of hemoglobin level; in all cases of immunogenicity comparative data are required for sc route. In comparative sc route studies, a total duration of twelve- months’ treatment is required.
- the clinical safety data are generally sufficient to provide a satisfactory data base for pre-marketing authorisation. The undesirable effects’ follow-up notably includes high blood pressure and its possible aggravation and thromboembolic events. The company must file immunogenicity data coming from a 12 months’ period for the biosimilar’s application file. A validated test sensitive to detecting early and late antibodies must be implemented during correction and maintenance phases. Searching for the presence of neutralising antibodies or Pure Red

Cell Aplasia episodes during the pre-authorisation phases is crucial; it must be complemented by an adequate post-MA follow-up. The data allowing to demonstrate a clinical similarity come from the comparative trial on the population considered the most relevant (chronic renal insufficiency), both in iv and in sc (on a number of patients big enough, as it is commonly accepted that the sc route is more immunogenic than the iv route);

- the typical pharmacovigilance program is completed by a risk management plan notably taking into account rare and serious secondary effects like Pure Red Cell Aplasia of immune origin and the EPO's potential action of tumour promoter;
- as EPOs' mechanism of action is identical for all approved indications for the reference product, and since there is a known EPO receptor, the demonstration of efficacy and safety in the chronic renal insufficiency population makes possible the extrapolation to other reference medicine's indications for the same route of administration.

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## Conclusion

The biosimilar approach based on an exercise of comparability with preclinical and clinical data, in addition to quality data, allow pharmaceutical companies to file a shortened file (compared to a standard complete file required for a new biotechnology-derived medicinal product) in order to obtain the MA of a biological product similar to the reference biological product; it is called a "biosimilar." It is more necessary to establish a given level of similarity in terms of quality issues than in terms of safety and efficacy, for the biosimilar to be approved in one or all indications of the reference medicine's. Biosimilars are above all biological medicinal products characterized by their own quality profile. The long-term consequences of possible differences between biosimilar and reference are not well known because the clinical trials, conducted over a short period, are designed to demonstrate the equivalence of efficacy and pharmacodynamics. The long-term safety profile will be known only after several years of these products' use. Because of that fact, a biological medicinal product cannot be substituted by a biosimilar medicinal product (as for standard generics) before having collected long-term data on efficacy and safety of the product in all populations to be treated. Currently, in France, the substitution of a biological medicinal product by a pharmacist is not possible. Only a medical prescription in controlled conditions may allow the substitution of a reference biological medicine by a biosimilar.

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## Further Reading

- Directive 2004/27/EC du Parlement européen et du conseil modifiant la directive 2001/83/EC instituant un code communautaire relatif aux médicaments à usage humain (31 mars 2004)

- EMEA/CHMP/437/04 Guideline on Similar Biological Medicinal Products (October 2005)
- EMEA/CHMP/BWP/49348/05 Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (CHMP adopted 22 February 2006)
- EMEA/CPMP/ICH/5721/03 ICH Topic Q5E Comparability of Biotechnological/Biological Products (CHMP adopted December 2004)
- EMEA/CPMP/ICH/302/95 ICH Topic S6 Step 4 Note for Preclinical Safety Evaluation of Biotechnology-Derived Products (CHMP adopted September 97)
- EMEA/CHMP/42832/05 Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical And Clinical Issues
- EMEA/CHMP/BMWP/31329/05 Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues. Guidance on Similar Medicinal Products containing Recombinant Granulocyte-Colony Stimulating Factor (CHMP adopted 22 February 2006)
- EMEA/CHMP/BMWP/94526/05 Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues. Guidance on Similar Medicinal Products containing Recombinant Erythropoietins (CHMP adopted 22 mars 2006)

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