MEMORANDUM

May 2014

Facts on switching between biological medicinal products (drugs) with the same mechanism of action and indications.

Introduction:
This document is based on published data relating to biosimilar drugs and addresses some of the issues that should be taken into account when switching from a biological drug that clinically suits a patient (original or biosimilar) to another biological drug (original or biosimilar).

The executive summary gives an overview of the content of the document followed by details thereof with associated source references.

Executive summary
The first biosimilar drug was approved in the EU in 2006. The introduction of biosimilars in the clinic has led to special considerations not observed in treatments with generic copies of chemically-based drugs and which therefore merit special attention. The reason for this is that biological drugs (mainly protein-based) are so large and complex that it is not possible to make a true copy but only a product that is similar to the reference drug to which it is being compared. Differences in the raw materials used, manufacturing processes and molecular characteristics can lead to therapeutic differences between biological drugs. In spite of this it does not appear from the name on the active biological substance (International Nonproprietary Names).

One special issue in biological proteins is that they are normally immunogenic, meaning that the patient may develop antibodies to the drug. This phenomenon may be insignificant but in some instances it can lead to changes in the efficacy and/or adverse reaction profile. Since even subtle changes in manufacturing processes can lead to changes in the product’s detailed structure, conformation and/or impurity profile, this means that biological proteins from different manufacturers may have a different efficacy and/or safety. Elucidating this problem usually requires separate non-clinical and always clinical trials.

For generic, chemical drugs, it is possible to use analytical methods to ensure an exact copy (full identity) between generic products and the original drug. But there are currently no sufficiently developed technological methods to determine whether two biological drugs are completely identical.

For a biosimilar drug to be approved by the authorities, the manufacturer of the biosimilar must therefore, in addition to having high product quality, generally conduct non-clinical and always clinical trials in accordance with the requirements imposed by the European authorities so as to ensure that the biosimilar drug’s safety and efficacy corresponds to the biological reference drug.
A biological drug (original or biosimilar) should only be used for the indication(s) for which the product concerned has been approved. In approving biosimilar drugs, the European Medicines Agency (EMA) considers whether the documentation submitted is sufficient for the biosimilar to be approved for use for all the indications applied for or only certain of them, as approved for the biological reference product.

In addition, the former Minister of Health and Prevention Astrid Krag has officially announced that public authorities ought not to recommend a medicinal product that is not approved for the concerned indication when a medicinal product exists that is approved for the concerned treatment.

On the basis of the above-mentioned conditions use of systematic off-label use shall be avoided.

In spite of the fact that biological and biosimilar drugs shall be approved by the European Medicines Agency, it is outside the remit of the agency to define guidelines for switching between biological products (original or biosimilar). This is a national matter that is decided by national authorities. The national authorities have access to all submitted data and all scientific evaluations carried out by the European Medicines Agency and thus have the necessary basis for documenting if it is recommendable to replace a biological drug with another (original or biosimilar).

It is important to be aware that it always should be the attending doctor who makes the decision about a possible switch.

Another significant issue with respect to biological drugs (original or biosimilar) is adverse drug reaction reporting. In order to ensure the best possible monitoring of these product categories, it is important when reporting adverse reactions to obtain detailed information about the specific product being used – i.e. data about the trade name, manufacturer and batch number, irrespective of whether the drug has been dispensed in a pharmacy or hospital.

There is a more detailed description below of the issues forming the basis for the above conclusions, including source references. The sections are designed to be read independently, why you will find some repetition in the individual sections.

- Introduction:
- Manufacturing biological drugs
- Approval of biosimilar drugs
- Indications
- Immunogenicity (antibody formation)
- Pharmacovigilance
- Switching between biological medicinal products

**Introduction:**

*Definition:*

The EU Medicinal product Directive, (Directive 2004/27/EC (amendment to Directive 2001/83/EC)) recognizes that there are fundamental differences between biological drugs
from different manufacturers, and it specifically states that biosimilar drugs are by definition not generics. The existing rules for generics are therefore not (immediately) applicable.

**Recital 15**

*Biological medicinal products similar to a reference medicinal product do not usually meet all the conditions to be considered as a generic medicinal product mainly due to manufacturing process characteristics, raw materials used, molecular characteristics and therapeutic modes of action. When a biological medicinal product does not meet all the conditions to be considered as a generic medicinal product, the results of appropriate tests should be provided in order to fulfil the requirements related to safety (pre-clinical tests) or to efficacy (clinical tests) or to both.*

**Article 10.2b)**

"*Generic medicinal product*" shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

**Article 10.4**

*Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal product, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these, conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product’s dossier shall not be provided.*

**Chemically-based drugs versus biological drugs.**

Chemically-based drugs such as acetylsalicylic acid and propranolol have small molecules that are easily replicable so that the properties of generic products are the same as the original product. Substitution can therefore be made between synonymous drugs of the same strength and usually the same form of drug (with certain exceptions) and where direct therapeutic equivalence or bioequivalence has been demonstrated.

However, this is not the case for biological drugs. Biological drugs are so complicated because of their large molecular size and complex structure that it is not possible to make an exact copy. Hence two biological drugs from different manufacturers can never be identical. But further non-clinical and clinical trials against an approved biological reference drug (the specific original drug) make it possible to determine similarity with the efficacy and safety profiles of the reference drug for authority approval. The extent of non-clinical and clinical trials with the biosimilar drug to show similarity with the reference drug depends on the biosimilar product concerned.
Examples:

<table>
<thead>
<tr>
<th>Product</th>
<th>Molecular weight (Dalton)</th>
<th>No. amino-acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>259</td>
<td></td>
</tr>
</tbody>
</table>

**Chemically-based drugs:**

**Biological drugs:**

<table>
<thead>
<tr>
<th>Product</th>
<th>Molecular weight (Dalton)</th>
<th>No. amino-acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin</td>
<td>4,500</td>
<td>32</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>22,000</td>
<td>191</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>30,000</td>
<td>165</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>264,000</td>
<td>2332</td>
</tr>
</tbody>
</table>

**Manufacture**

There are major differences in the manufacture of chemically-based drugs and biological drugs respectively, with the latter mostly being protein-based drugs.

- Chemically-based drugs are made by mixing chemicals and reagents together in controlled and predictable chemical reactions.
- Biological protein-based substances are made by "harvesting" the protein that is produced and secreted by a living organism, for example a bacterium or a yeast cell.

The characteristics of chemical substances are therefore well-defined and drugs from different manufacturers can be tested and compared in the laboratory using known, predictable analytical methods. It is therefore possible to make fully identical substances of this type.

The properties of biological drugs are affected by the equipment, raw materials, process parameters and the analytical methods used to control the processes. The properties of any biological drug may therefore be affected by the actual production process. Biological protein-based drugs from different manufacturers may vary in structural details and conformation, glycosylation, derivative/ degradation products and presence of miscellaneous impurities. Even though these properties can be separately measured using a range of different analytical methods, it is not possible to have full 100% quantitative comparability for all variants, and there are also no methods for predicting what impact these properties may have on the efficacy of a product or its influence on patient safety.

One special issue in biological proteins is that they are normally immunogenic, meaning that the patient may develop antibodies to the drug. This phenomenon may be insignificant but in certain cases it can lead to changes to efficacy and/or the development of adverse reactions. Since even subtle changes in manufacturing processes can lead to changes in the product's detailed structure, conformation or impurity profile, this means that biological proteins from different manufacturers may have a different efficacy and/or safety.
Biological drugs (mainly protein-based) are so large and complex that it is not possible to make a true copy but only a product that is similar to the reference drug to which it is being compared. Differences in the raw materials used, manufacturing processes and molecular properties can give rise to differences in safety between a biosimilar and a reference drug.

There is the requirement for continuous optimisation of manufacturing processes for all drugs. The manufacturers of all biological drugs (original or biosimilar) are required to undertake comprehensive studies to gain authority approval for manufacturing changes to ensure that the biological drug concerned (original or biosimilar) continues to have the same properties as the original approved drug.

**Approval of biosimilar drugs**

All biological products (original or biosimilar) submitted after 1 January 1995 requires approval by the European Medicines Agency via the centralised procedure.

Approval of biosimilars requires pharmaceutical, often non-clinical and always clinical documentation to confirm that the two products are comparable within further specified specifications. In contrast, generics based on small molecules can be approved without other clinical studies than bioequivalence studies since it is possible to demonstrate that they are identical with the reference product.

The EU Medicinal product Directive states the conditions that must be met to be able to obtain approval for a biosimilar product. Accordingly, supplementary information must be submitted to demonstrate that the non-clinical and clinical profile corresponds to the reference drug (an original product). The EMA has drawn up scientific guidelines setting the requirements for the documentation to be provided for various types of biosimilar drugs. There are constant official assessments to identify whether certain more recent groups of products require their own biosimilar guidelines.

**Directive 2003/63/EC of 25 June 2003, Annex 1, Part II. Section 4**

- "Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.

- Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.

The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency. In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.
**Indications**

Biosimilars may be approved in certain instances for fewer indications and/or administration forms and/or routes than the reference drug. This may be due to the fact that the manufacturer has not applied for all of these for commercial reasons or that there has not been sufficient documentation to obtain these.

Differences in the three dimensional structure or impurity profile can mean that the biosimilar drug only possesses certain of the properties of the reference drug. Systematic off-label use should therefore be avoided when treating with biological drugs.

The EMA determines the number of non-clinical and clinical trials for biosimilar drugs required for each indication. This means that extending an indication for a biological drug may not automatically be approved for another biological drug, including a biosimilar product with a similar active agent, without the existence of solid medical arguments.

The Minister for Health and Prevention has in her answer to S 826 of September 9, 2013 related to public authorities’ recommendations on “off-label use” in general guidelines etc.

It appears from the minister’s answer that:

"Therefore public authorities, according to the ministry’s opinion, ought not to prepare general recommendations specifying that, as a rule, for a specific treatment (i.e. without identification of individual therapeutic needs in a specific patient) a specific medicinal product shall be used that is not approved for the concerned indication.

This interpretation applies in cases where another medicinal product that is approved for the relevant indication is available at the Danish market. No other situations are considered e.g. where there is no alternative medicinal product approved for this indication, or if a medicinal product approved for the indication is not tolerated or has been used without any effect."

Click here to read the minister’s answer (in Danish):

**Immunogenicity (antibody formation)**

Practically all biological drugs (original or biosimilar) are immunogenic, i.e. the patient may develop antibodies against the drug. The prevalence of antibodies varies from extremely rare to occurrence in more than 50 percent of patients. At the present time it is not possible to predict the formation of antibodies and nobody knows the significance of the actual increase, a fact that will only become apparent in the longer term. The immunogenicity of biological drugs (original or biosimilar) can only be assessed by way of non-clinical and clinical trials and post-marketing product surveillance.

The effects of antibody formation are due among other things to patient and disease-related factors, genetic factors, treatment with other drugs, administration roots and drug formulation.
The clinical significance of antibody formation may vary from a) being insignificant b) altering the therapeutic effect of the drug or c) leading to serious adverse reactions.

The more rare adverse reactions include problems of antibodies to biological drugs cross-reacting with endogenous factors and this can lead to serious toxicity if the endogenous factors have a significant biological function. This fact has for example been illustrated by an increase in the incidence of "Pure Red Cell Aplasia", which is a serious though extremely rare type of anaemia in patients being treated with recombinant erythropoetin. The increase was caused by changes in the formulation of the biological products – see Example 1 below.

The examples given below are sourced from scientific journals.

**Examples:**

1. **Change of formulation and administration led to pure red cell aplasia in patients receiving EPO treatment:**
   Following change of formulation of Eprex a group in Paris identified 12 EPO-treated patients with antibody-mediated Pure Red Cell Aplasia (PRCA); 11 of these patients were on hemodialysis and had received subcutaneous Eprex (Johnson & Johnson). In 2002, authorities in Europe, Australia, Singapore, and Canada mandated Eprex by IV route to hemodialysis patients, and the relevant manufacturers added Teflon coating to prefilled syringes of Eprex; PRCA cases subsequently decreased by 90 percent. By 2003, 180 Eprex-associated PRCA cases were identified in Europe, Canada, Australia, and Asia, despite improvements in handling. Since 2002, FDA safety databases include information on 59 new cases of antibody-associated PRCA, primarily associated with subcutaneous epoetin alfa and darbepoetin that does not contain HSA. (Transfusion 2008, Aug 48 (8) 1754-62).

2. **Interferon (IFN) beta for treatment of Multiple Sclerosis (MS(s))**:
   Three different IFN beta reparations are currently used for the treatment of patients suffering from MS. Two of the preparations IFN beta-1a has identical amino acid sequence, while two substitutions are observed in IFN beta-1b. These minor differences in preparation, formulation, administration, etc., have led to significant differences in the immunogenicity of the products. Antibodies induced against one preparation usually cross-react with the other preparations (Ross et al, Ann Neurol 2000, 48(5) 706-12).

3. **Others:**
   Furthermore some companies have observed issues regarding immunogenicity in the post marketing phase (e.g. Roceron® (IFN alpha-2a, Roche) and Rebif® (IFN beta-1b, Serono) resulting in follow up modifications of formulation in order to reduce immunogenicity) (various sources).

**Pharmacovigilance**

It is important, especially when using biological drugs (original or biosimilar), to be able to identify and trace the specific product being administered (trade name, manufacturer and batch number) in case adverse reactions occur during treatment. This reflects the risk of immunogenic reactions and possibly changes to efficacy/dosage.

This is accordingly specified in the overall guideline on biosimilar drugs ("Guideline on Similar Biological Medicinal Products, CHMP/437/04 of 30 October 2005").
“It should be recognized that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established. Therefore in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified.”

Since there are no methods that can predictively determine the impact of even small production related differences on a drug’s efficacy and safety, the general provisions on pharmacovigilance state that it is important when using biological drugs that the product prescribed for the patient concerned should always be precisely identifiable (trade name, manufacturer and batch number). This applies to drugs dispensed by pharmacies as well as hospitals, and in case this information is not available in an adverse reaction report it is required that the marketing authorisation holder shall seek to gather information subsequently.

In directive 2010/84/EC amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use the following are specified:

Article 102 e) The member states “ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, in accordance with Article 1(20), and the batch number”.

Further specification is indicated in guideline on good pharmacovigilance practices (GVP), Module VI B 3: as follows:

“For suspected adverse reactions relating to biological medicinal products, the definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the name of the product and the batch number”. A business process map in relation to the mandatory follow-up of information for the identification of suspected biological medicinal product is presented in VI.Appendix 1”.

Switching between biological medicinal products

The possibility for switching between a biological medicinal product (original or biosimilar) is outside the remit of the European Medicines Agency. This is a national matter that is decided by the national authorities. The national authorities have access to all submitted data and the agency’s scientific evaluations, and by this they have the necessary basis for documentation of whether it can be recommended to replace a biological medicinal product with another (original or biosimilar).

As noted in the section on "manufacture," it is a core feature of chemically-based (generic) drugs that the chemical structure of the active substance in the generic drug is the same as in the original drug and that there are methods which can demonstrate this with total certainty.
It is therefore an option for chemically-based drugs for substitution to be made between synonymous drugs of the same strength and usually the same pharmaceutical form and where direct therapeutic equivalence or bioequivalence has been proven. This substitution takes place at a pharmacy without consulting a doctor and on the basis of lists prepared by The Danish Medicines Agency. In contrast, there are no sufficiently advanced technological methods to fully prove that various biologically made drugs are completely identical. Biologic similar drugs are thus similar to the original reference drug, but not identical to it. The small variations between protein-based drugs can lead to differences in the biological and chemical properties meaning that the existing rules for generics cannot be applied, including the option of substitution.

In connection with switching between biological medicinal products these terms are used: interchangeability and switching that are defined in the following way in the EU Commission’s Consensus Information Paper 2013, What you Need to Know about Biosimilar Medicinal Products (the Commission Report):

“Interchangeability: The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with an agreement of the prescriber.”

“Switching: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.”

Switching backwards and forwards between differently manufactured biological protein-based drugs may lead to special risks for individual patients because of the potential risk of serious antibody reactions (immunogenicity) and should therefore be avoided. In instances where a change is necessary, it should be done with the prior agreement of the attending physician and a specific assessment of the individual patient.

It appears from the Commission Report that:

- “The decisions on interchangeability and/or substitution rely on national competent authorities and are outside the remit of the EMA/CHMP. Member States have access to the scientific evaluation performed by the CHMP and all submitted data in order to substantiate their decisions”.

- “For questions related to switching from one biological medicine to another, patients should speak to their doctor and pharmacist”.

Corresponding information is published on the European Medicines Agency’s web site – click here.

It should also be noted that because of the above-identified differences between biological drugs (original and biosimilar), these should always be prescribed under their trade name cf. article 102 e) in directive 2010/84/EC above.

In deference to patient safety, various European member states have used national legislation to prohibit automatic substitution for biological drugs or have given advice on the use of biological drugs (including description under the trade name).
References:

Pharmacovigilance legislation published on the European Medicines Agency’s web site.