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Thirty years ago the first biotechnologically manufactured medicines were introduced to the market. Since then, a wide range of these biopharmaceuticals has followed, including hormones, growth factors and antibodies. Biopharmaceuticals are produced inside bacterial, fungal, plant, animal or human cells. This makes the manufacturing process very special and different from traditional (chemical) pharmaceuticals. Nevertheless, just like these traditional medicines, biopharmaceuticals are protected by patents that prohibit copying. Once the patent period has expired (after 20 years), companies can put their own versions on the market, the so-called biosimilars. Unlike chemical medicines, it is not possible to make an exact copy of a biopharmaceutical. Because of the biological production process, each biopharmaceutical (and each biosimilar) has unique properties. This has consequences for patient use.

With the information in this brochure, we would like to explain the nature of biosimilars and what it means for patients and caregivers. In the coming years an increasing number of biosimilars will become available. Therefore, it is important to be well informed.

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The first biological medicine was approved for human use 30 years ago. Since then, many new biopharmaceuticals (biologics) have reached the clinic and the patient. It is forecasted that biopharmaceuticals are to become the biggest selling products by 2016. Following patent and exclusivity expiry on innovator biologics, subsequent versions of these products may be produced by a different company. In the past few years the first versions of these so-called biosimilars have entered the market. Biosimilars might be cheaper than the original molecules, but are they as effective and safe?

Biopharmaceuticals and biosimilars

Chemical medicine
(Conventional medicines)
• Manufactured using defined chemical process steps (synthetic process)
• Simple chemical ingredients
• Uniform, predictable structure that is easy to characterise
• Typically offered in tablet or capsule form

Biological medicine (biological)
• Manufactured using a biological system (living cells)
• Large complex protein
• Complicated three-dimensional structure with greater degree of heterogeneity and associated difficulty to characterise
• Typically offered as a liquid (injection or infusion)
Biopharmaceuticals

Biopharmaceuticals are produced in living cells. They consist of human proteins, such as antibodies, hormones and cytokines, fragments thereof and other substances. The large majority of biologicals is produced in special cells, which are genetically modified and grown in special fermentors. Biotherapeutics differ in many ways from conventional (chemically produced) medicines, for example in manufacturing techniques, molecular size and complexity, stability of molecules and clinical properties.

As with all innovative medicines, biopharmaceuticals are protected by patents for a period of 20 years. During this period, all the necessary research in the lab, tests on animal models and trials in patients have to be carried out. If all of this leads to positive results the medicine can be registered, and the final time-consuming process of reimbursement can begin. Only after that has been completed is the medicine actually available for the patient. On average, 10-12 years of the patent protection period has expired by then. Once the patent protection period has ended, other manufactures can use all the research results and acquired knowledge pertaining to the original biopharmaceutical to demonstrate similarity to a reference product and thereby gain market approval.
Biosimilars

A biosimilar is a medicine that is modelled on the original biopharmaceutical (the biological reference product); however, it is not identical to it. The production process of biopharmaceuticals varies from one manufacturer to the next and as a consequence every biopharmaceutical has unique properties. Small differences from the original production process can result in variations in the complex structure of the protein and thus to differences in efficacy and/or safety. Just like other (biological) medicines, biosimilars can only be marketed after they have been registered. Biosimilars are manufactured according to the same standards as other biopharmaceuticals and are safe and effective. Because biosimilars are not exactly identical to the reference medicine, the proven safety profile of that reference medicine cannot be claimed. As a result, a biosimilar cannot be substituted for the biological reference medicine or another biosimilar. Thus a preferential policy regarding biopharmaceuticals and biosimilars is not possible, as this policy is based on the principle of medicines having ‘the same active ingredient’. Furthermore, a characteristic of the preference policy is automatic substitution; this means that a pharmacy will give a patient a medicine that is different from what was prescribed by the doctor, without the doctor or the patient being consulted.

Production of biopharmaceuticals

The production of biopharmaceuticals is much more complex than that of chemical medicines. There are a number of reasons for this, including the nature of the starting material and the exceptionally high level of accuracy required by the production process. The production of every biological medicine begins with the design of a unique cell line that will serve as a production platform: the master cell line. The starting point of this master cell line are cells (microbial, animal or human), which can multiply under certain specified conditions. Using molecular biological techniques, DNA is introduced in cells in order to produce the desired protein (on page 13). This creates a unique master cell line, which can never be exactly reproduced by others. This is one of the reasons why another manufacturer of biopharmaceuticals can never exactly reproduce a biological medicine: every manufacturer has its own unique master cell lines.

The final production of a medicine entails:
(a) the multiplication of the cells
(b) the production of the desired protein and
(c) the harvesting, purification and possibly further treatment of the produced substances.

Factors like these determine not only the structure and yield of the end product, but also the amount of interfering or undesirable
by products. For this reason each and every biopharmaceutical production installation is unique: a change in only one of the hundreds of steps in the production process can influence the end result. In extreme cases it can necessitate a new legal production permit.

During the production process cell growth and fermentation are important. Even the smallest of variations in the manufacturing process (such as in temperature or components of the growth medium) can lead to significantly altered physical and clinical properties of the final biological medicine, change the yield of the end product or the amount of interfering or undesirable byproducts. The exact conditions during purification and processing of the produced substances are equally important. For these reasons each and every biopharmaceutical production installation is unique: a change in only one of the hundreds of steps in the production process can influence the end result. In extreme cases changes can necessitate a new legal production permit.

It is therefore essential that the production process and environment in the production installation be kept constant in order to ensure consistent results and to guarantee the safety and efficacy of the final product. The production of biological medicine, therefore, requires a high level of monitoring as well as scores of quality tests. During the production process of a biopharmaceutical typically 250 quality tests are carried out, compared to around 50 for chemical medicines.
A biosimilar is an imitation of another biological medicine-referred to as the ‘biological reference medicine’- that can be marketed after the patent and the legal data protection expire. A biosimilar is not a copy. Biopharmaceuticals have a complex three-dimensional structure, which makes production of an exact copy difficult. The production process of a biopharmaceutical has small variations that lead to small but controllable deviations between different production batches of a biological medicine. Therefore, the manufacturer of a biopharmaceutical will test every batch of a biological medicine individually for product safety.

Manufactures of biosimilars use their own (and thus different) master cell lines, culture conditions, raw materials, and purification techniques. This significantly increases the biological variations. Besides the small variations between batches there are greater differences between a biosimilar and the biological reference medicine. For instance, it matters greatly whether a biopharmaceutical is made using bacteria or a human cell line. These differences can have major consequences for quality, effects and side effects of a biosimilar. Furthermore, different additives are often used for the biosimilar than for the biological reference medicine.

What are biosimilars?

Authorisation requirements

The healthcare sector has been using generic medicines for decades. For generics the active ingredient is an exact copy of the chemical compound of the originator medicine. Authorisation to bring a generic to the market is fairly simple: manufactures are not required to do animal testing nor clinical trials with patients to show safety and efficacy of a generic medicine. Because the generic contains an exact copy of the active ingredient of the reference medicine manufacturers can refer to the authorisation dossier of the reference medicine.

Biosimilars follow a different, but also accelerated procedure of market authorisation at the European level. However, because the equivalency to the original biological medicine cannot be fully established, the safety and efficacy of a biosimilar cannot be based entirely on the animal experiments and clinical studies of the biological reference medicines. Before a biosimilar can be marketed, they are subjected to limited clinical studies with patients to determine whether the effects of the main use of the biosimilar are equal to the reference medicine. A biosimilar is, therefore, in fact a new product that on the basis of limited studies is given authorisation for a very specific indication.
## Authorisation differences between generic medicines and biosimilars:

<table>
<thead>
<tr>
<th>Generic medicines</th>
<th>Biosimilar</th>
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<tbody>
<tr>
<td>‘Essentially equivalent’ to the reference medicine, assessment/judgement of interchangeability</td>
<td>‘Similar’ medicine; no assessment/judgement of interchangeability with biological reference medicine, it is only assessed whether there is similar efficacy and safety.</td>
</tr>
<tr>
<td>Identical active (chemical) substance/compound</td>
<td>Similar but not identical active substance/compound</td>
</tr>
<tr>
<td>Identical pharmacological activity</td>
<td>Similar biological activity uncertain</td>
</tr>
<tr>
<td>The absorption in the body (‘biological availability’) needs to researched</td>
<td>Determination of bio-equivalence is not usually possible or sufficient for authorisation.</td>
</tr>
<tr>
<td>Determination of bio-equivalence is sufficient for authorisation, own animal testing and clinical trials not necessary</td>
<td>Additional information is required for authorisation, in particular with regard to the toxicological and clinical profile (‘comparability exercise’); the necessary information varies from case to case and depends on the active compound/substance (protein)</td>
</tr>
<tr>
<td></td>
<td>The efficacy and safety of a biosimilar must not be adequately motivated or demonstrated for every requested indication. Extrapolation is possible in principle.</td>
</tr>
<tr>
<td></td>
<td>Depending on the type of biosimilar after authorisation extra safety studies are mandatory (‘post-authorisation safety studies’, PASS)</td>
</tr>
<tr>
<td></td>
<td>Pharmacovigilance demands traceability of an individual medicine at a detailed level (individual patient, brandname, batchnumber)</td>
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<tr>
<td>In principle no extra safety studies are required after authorisation</td>
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<tr>
<td>Simple pharmacovigilance</td>
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As seen from the overview, biosimilars and biopharmaceuticals need specific registration requirements, depending on the type of active substance/compound. Furthermore in the registration dossier specific additional data need to be included to allow a ‘comparability exercise’. For instance, specific requirements exist for biosimilars of biopharmaceuticals consisting of monoclonal antibodies (mAb). However, contrary to what one might expect, it is not necessary for a manufacturer of a biosimilar to demonstrate safety and efficacy in all cases. This is not necessary for every indication or for every phase of treatment (e.g. in oncology in the early stage of the disease as (neo)adjuvant treatment or in the metastatic stage of the disease). An extrapolation of the clinical efficacy and safety data to other indications of the reference antibody is sometimes possible on the basis of the assessment by the European Medicines Agency (EMA) of the total evidence stemming from the ‘comparability exercise’ and with adequate justification. In those cases it is considered sufficient when only the most vulnerable patient population and the clinical endpoint is studied. The reason for this is to identify any product related differences. For studies using biosimilars with monoclonal antibodies, for example, it is not necessarily required to use ‘overall survival or a ‘progression-free survival as end point.

Guidelines of the EMA state that reports on side effects of biopharmaceuticals must always include the brand name, the manufacture’s name and the batch number of the given medicine. Therefore it is essential that all biopharmaceuticals be prescribed using the brand name and not the name of the compound/substance (international non-proprietary name (INN)). This holds true for biosimilars as well. Manufactures are also required to have a risk management plan in place for every biological medicine. Among the reasons for this is the fact that the immune systems of patients may respond differently to different biopharmaceuticals, even to those with the same compound/substance name. Moreover, biological reference medicines and biosimilars may not be registered for the same indications and may have other dosing regimes or different side effects. And, at the end of 2012, the European Commission has has issued a directive which requires biological products to be identified by brand-name and not by INN.
Interchangeability of a medicine refers to a situation where a medicine can be exchanged for another equivalent product (with a proven equivalent efficacy and side-effect) at the patient level. The pharmacist can ‘exchange’ an interchangeable medicine without significant risk for an adverse health outcome. Because of the unique chemical and biological make up of a biosimilar it is not automatically interchangeable with the reference product. An assessment of the interchangeability is not part of the scientific assessment by the EMA. Therefore, no conclusions can be drawn concerning the interchangeability or automatic substitution of biopharmaceuticals on the basis of the granted market authorisation. Furthermore, there are no clinical studies that have evaluated whether repeated switching between two biopharmaceuticals has any unforeseen effects. Various scientific associations have indicated not wanting to run these potential risks when there are no compelling medical reasons.

Biopharmaceuticals are often used for seriously or chronically ill patients. Undesirable effects arising from the switching between non-identical medicines should always be avoided. Of course, biopharmaceuticals also have side effects; sometimes these appear while using the medicine. In other cases they do not appear until after the treatment. Because of their specific properties biopharmaceuticals can lead to a response of the immune system of a patient. This can have consequences for the safety and efficacy of that medicine. Therefore, during the clinical trials of a biological medicine this is monitored very carefully. But even after registration, companies are required to develop and implement a pharmacovigilance plan for their biopharmaceuticals. An aspect of this is traceability, so that it is absolutely clear which patient at what time received what medicine. In order to trace which medicine is responsible for the undesirable side effects (e.g. an immune response), the physician needs to know which biological medicine was given and when it was given to the patient. This traceability is an essential requirement for biopharmaceuticals. The automatic exchanging of different medicines by pharmacists (automatic substitution, resulting from the preference policy) complicates this traceability and because of this is medically undesirable.
According to the EMA biosimilars and biological reference medicines are similar but not identical. For this reason, the decision to treat a patient with a biological reference medicine or a biosimilar must be based on the assessment of a qualified ‘healthcare professional’. In The Netherlands this is the attending physician. The Medicines Evaluation Board (MEB) is of the opinion that patients, as much as possible, should remain on the same biological medicine when they are responding well and that a switch to another biological medicine should be avoided. Moreover, a switch may only occur under the strictest conditions, including the attending physician’s approval. Uncontrolled switching (switching without adequate monitoring) between biopharmaceuticals should be avoided, regardless whether it concerns originator or biosimilar medicines. However, if exchanges do take place the patient record must detail specific information (brandname and batch number), so that traceability of a product is guaranteed in the event of a problem.

Prices and the impact on the healthcare budget

After the patent period for a biological reference medicine expires, other manufactures can develop and market biosimilars. Some healthcare stakeholders still are under the assumption that the introduction of these biosimilars will lead to substantial price advantages. However, these price reductions cannot be compared to the situation after the introduction of generic medicines. There are several reasons for this. First of all, biopharmaceuticals are more complex than chemical medicines and development and production of biopharmaceuticals is more expensive and time consuming. The development of a biosimilar can take up to between seven and eight years, with costs in the order of € 60 to €200 million (compared to two to three years for a generic medicine, with a price tag of €1.6 to €2.4 million). In addition, the requirements for market authorisation and post-marketing surveillance for biosimilars are stricter than those for generic medicines. The exact price of a biosimilar also depends on the number of market competitors (biosimilars as well as the biological reference medicines and other innovative biologicals) and the pricing and reimbursement regime of a country.
What do biosimilars mean for...

Patients
Patients should be fully informed about each medical treatment they receive. A patient should be involved in any decision concerning the prescription of a particular medicine and understand why that decision was taken. In the future patients will be using more and more biosimilars. This can lead to situations whereby physicians prescribe another medicine than what the patient is used to. In this case, patients need to be alert to more and different side effects and should contact their physician immediately in such events. Furthermore, biosimilars can be offered in a different packaging or form than that of the biological reference medicine, which can be confusing for patients and have a negative impact on therapeutic compliance/patient confidence in a therapy.

Physicians
In the healthcare system only doctors diagnose patients and provide them with the appropriate medicine. The doctor may decide, in consultation with a patient, to use a biosimilar. Central to this is the treatment outcome. Therefore it is necessary that doctors follow their patients carefully, so that decreased efficacy or side effects that emerge can be noticed quickly. Physicians should be aware that registration authorities have not evaluated the interchangeability between biosimilars and biological reference medicines. Furthermore, it is important to realise that the registration process of a biosimilar is essentially different from that of the biological reference medicine. In order to make a correct decision the physician needs to have all the relevant information on the biological reference medicine and the biosimilar. This includes information about which applications are supported by clinical studies and which are only inferred through extrapolation.

Pharmacists
The pharmacist cannot independently deviate from a doctor’s prescription, even if he/she believes that there is a pharmacomedical reason. A pharmacist cannot, on his/her own initiative give a patient a biosimilar medicine in place of the biological reference medicine. Pharmacists need to take into account that biologicals with the same compound/substance name (international non-proprietary name (INN)) are not interchangeable. This is different from (many) generic medicines. Pharmacists need to realise (just as doctors), that the interchangeability between biosimilars and the reference medicines, as well as clinical efficacy...
for extrapolated indications, is not (necessarily) evaluated by the registration authorities. Recently, the EU has issued a directive which requires biological products to be identified on recipes by brand-name and not by international non-proprietary name (INN).

**Health Insurers**

Many health insurers have designed active policies to stimulate the use of biosimilars. They refer to possible price advantages between biologicals and biosimilars. However, the cost of a medicine is not the only parameter that determines its effectiveness. Furthermore, The Netherlands already has several systems by which the ‘price spiral’ of similar drugs is adjusted downward. A case in point is the law governing the prices of medicines (Wet Geneesmiddelenprijzen or WGP) under which the Minister of Health examines, twice a year, whether the maximum price needs to be recalibrated; in which case the average price of similar medicines that are included in the price lists of four reference countries determines the maximum price in The Netherlands. The Order of Medical Specialists has issued a guideline for effective prescription and regular updating of medical treatment guidelines takes place, in which effectiveness of the different medicines is specifically taken into consideration by the authors (attending physicians). Finally, the transfer in the coming years of many of these medicines from the GVS to the performance medical care (DBC/DOT) is expected to lead to lower wholesale prices as a result of market mechanisms [read: negotiations between hospitals and producers of medicines].

**The authorities**

Recently, new European rules have been introduced concerning the pharmacovigilance of biopharmaceuticals (including biosimilars), to ensure that any adverse effects of treatment are recognised faster and can be better followed. The national authorities are required to ensure that biopharmaceuticals within their borders are traceable on the basis of detailed information (as product name and batch used). In December 2012 the European Commission has published rules that require biopharmaceuticals to be identified by brand-name and not by INN.