

## **Bio.be Position Paper on naming and prescription rules for biological medicinal products**

### **1. Background information:**

#### **What are biological medicinal products and how are they manufactured?**

Cloning of human genetic material and development of in vitro biological production systems during the past 25 years has allowed the production of recombinant DNA based substances for eventual development of a drug. Monoclonal antibodies technology combined with rDNA technology also paved the way for tailor-made and targeted medicines and therapies. These biological medicines, based on the science of biotechnology, are clearly to be distinguished from the classical chemical drugs (small molecules) which are based on the science of chemistry. They often provide patients a substance or a process that occurs naturally in healthy people.

Biological medicinal products are made applying these biotechnology techniques in a tailored manufacturing process. They are made using living cells – each cell, like each person, is unique – hence each product is unique. Biological medicines are manufactured under very controlled conditions, as they are highly sensitive to the manufacturing process. Small changes in the way that products are made can dramatically alter their safety or efficacy. The different specific steps in the manufacturing process are the developing of the host cell, the establishment of a cell bank, the protein production, the purification (the most expensive step), the analysis, the formulation and the storage and handling. Even very small process changes such as small variations in temperature (cell) culture conditions or even transport or storage conditions can result in significant changes in clinical properties of the resulting product, thus potentially affecting its efficacy and safety. The production of biological medicinal products therefore requires a high level of monitoring and quality checks. The efficacy and safety aspects of a biological medicine are intrinsically linked to the actual manufacturing process of the product. This differs from the process of manufacturing chemical medicines, which makes up the majority of pharmaceuticals and healthcare treatments. Chemical ingredients are combined in a process to produce the final drug or pill. The structure of a chemical medicine is simpler, the ingredients of the drug are identifiable, can easily be characterized and their process of production is easier and can therefore be replicated easily. It is therefore possible to make an exact identical copy of a chemical drug, such as the case for generic drugs. The biological medicine is very complex, cannot be easily characterized, is highly dependent on the manufacturing process, and cannot be easily replicated. Since biotechnology manufacturing processes are covered by intellectual property, they cannot be copied.

#### **What are biosimilars medicines and how do they raise new issues?**

The expiry of the patents and the data protection periods for the first approved biological medicinal products has led to the development of what are called “biosimilars”. These are products that attempt to copy an original innovative biological medicine. In contrast to the development of copies of chemical medicines, a process which is relatively straightforward, it is not possible to make an identical copy of biological medicine due to its complex structure, unique cell line and tailored manufacturing process. The resulting products are only similar and not identical, and their introduction into clinical practice presents new challenges that are

not ordinarily presented by small-molecule generic medicines. Biosimilars cannot be described as 'generic version' of the original biological medicine. They may have different clinical characteristics that cannot be detected through pre-market testing e.g. rare adverse events (especially immune mediated events) or medically significant increases in such events. The critical factors for the occurrence of immunogenicity are a different amino acid sequence, a different glycosylation, a different formulation process or different storage or handling/manipulation (which can have an impact on aggregate formation).

The specific nature of biosimilars has recently led the European Union to establish a new legislative pathway for approval of biosimilars. The Directive 2004/27/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use lays down the requirements for the Marketing Authorization Applications (MAAs) based on the demonstration of the similar nature of the two biological medicinal products. Approval for biosimilar medicines must pass through the European Medicines Agency (EMA). As it is not possible to demonstrate that two biological medicinal products are identical, the presumption of the legislation is that preclinical/clinical data need to be individually defined.

Comparability studies, including appropriate original pre-clinical and clinical studies, are needed to generate evidence substantiating the similar nature of the new similar biological medicinal product and the chosen reference medicinal product already authorized in the Community. Strong pharmacovigilance programs need to be implemented post-approval in order to assure the safety of biosimilars, for instance to detect any abnormal immunogenic adverse events, and their Summary of Product Characteristics needs to be updated as soon as new efficacy or safety data become available. Besides changes in the manufacturing process which alter the biological activity of biological medicines, the possibility for inconsistent quality and potency, contamination with endotoxins (related to the purification process) and presence of excess aggregates are a concern and need continuous pharmacovigilance and the need for a risk management plan.

In order to give further clarity to the process, the EMA has published a set of 5 final guidelines on biosimilars which provide guidance on quality, non-clinical and clinical issues. Some product class specific annexes to the guideline on non clinical and clinical issues have also been released recently.

All these regulations and guidelines have now come into effect and to date, two biosimilars have been approved and granted an EU marketing authorization.

## **2. Naming of biological medicinal products**

The INN system is an international nomenclature administered by the World Health Organisation which lays down guidelines to grant a unique name for each pharmaceutical active substance. It was first introduced in 1950 for chemically derived active substances that can be characterized unequivocally by a chemical name or formula and exceptions to this rule were rare. The aim of the INN nomenclature is to provide health professionals with a unique and universally available designated name to identify a pharmaceutical substance and ensure the safe prescription and dispensation of medicines.

This system assumed that it was possible for an active substance made by different manufacturers to be proved to be identical by the available analytical tools and that their effect on the patients will therefore be the same. A pharmaceutical active chemical substance will therefore have the same name whether the active substance is contained in an original pharmaceutical specialty or in a generic product.

The arrival of the first biotechnology derived medicines did not dramatically change the nomenclature system. Since the time in the early 80's that insulin human became the first INN for a recombinant product, the range of biological medicinal products has increased in size and complexity. Even though it was originally developed to be applied to chemical, well defined substances, the INN system has adopted a specific system using common stems or substems for particular groups of biological compounds associated with their physiological

actions. For example, the stem 'som' is used for growth hormones, 'stim' for colony stimulating factors, etc. Prefixes and suffixes have also been selected to distinguish products within a same category and Greek letters can differentiate proteins according to their glycosylation patterns. There are for instance 7 different products with the same name 'epoetin' each followed by a different Greek letter and all have the same molecular formula.

However the arrival of biosimilars further increases the complexity and possible confusion in names. The general principle that products with a same INN are identical is no longer met as biosimilars are, by nature, similar but not identical as they cannot be an exact copy of the reference biological product.

INN's of the first biosimilars approved in Europe are identical, somatropin, and refers to two products made by two distinct manufacturers which also contain somatropin as an active ingredient. Confusion is growing even more when it appears that biosimilars of epoetin (a recombinant protein stimulating the erythropoiesis) that are in development can have, according to their manufacturer, either the same name as their reference product e.g. epoetin alfa, or a different name, e.g. epoetin zeta, another biosimilar also using epoetin alfa as the reference product.

These issues have led different industry associations to call for change in the nomenclature so that distinct INN names are assigned to biological products. A workshop held in November 13 has been especially set up by the WHO to address this issue. A consultation process has been initiated and may lead to a clearer position from WHO on naming of biological medicines. WHO is aware that INN is not used appropriately in prescribing and dispensing and will issue communications to define the role and limitations of the INNs. The process of updating the INN system is underway, but any change to the INN system will take time

### **3. Importance of the proper identification of the biological medicinal products.**

Three key issues related to the identification of biosimilars have been identified: pharmacovigilance, substitution, and traceability. These mainly derive from the following requirement in the CHMP guideline CHMP/437/04 ("biosimilar guideline"):

"..in order to support pharmacovigilance monitoring, the specific product given to the patient should be clearly identified".

Bio.be fully supports this statement and believes that the lack of proper identification for biological medicinal products, including biosimilar medicines could create public health concerns for the following reasons:

- **Pharmacovigilance issues:** the generation of meaningful pharmacovigilance information in the European Union will be facilitated if each biosimilar medicine is assigned a unique identification to distinguish it from other biosimilar products and from the innovator's product. Having multiple biosimilar products of a certain innovator product on the market without a proper identification system could lead to inadequate reporting of safety events that could be wrongly attributed to a particular manufacturer. This could lead to a dilution of messages about safety.
- **Substitution issues:** by contrast with the situation applicable for generics or "copies" of small molecule drugs, biosimilar medicines are "similar" but not "identical" to the innovator reference products. The "similar, but not identical" nature of biosimilar medicines means that substitution of the innovator product with a biosimilar product could have clinical consequences as patients could respond differently to the two products. Clear identification of biological medicines could provide a safe mechanism for ensuring the patient is dispensed the precise medicine prescribed by the physician.
- **Traceability issues:** an identification system that distinguishes between manufacturers could significantly reduce the risk of errors or confusion in medication,



prescription, or distribution of biotech medicines, ensure appropriate traceability for the quality of the product, and ultimately increase the safety of patients.

As prescription and substitution rules are mostly regulated at national level in each EU member state, in light of these potential issues, bio.be has looked at the implications in the Belgian regulatory context.

#### **4. Prescription by INN: specific issues in the case of biological medicinal products in the Belgian context**

Based on above considerations, bio.be believes that healthcare professionals should always make an informed clinical and medical judgment when prescribing a biological medicinal product, i.e. deciding which brand to prescribe in case several exist for a given indication, whether to prescribe a biosimilar medicine or whether to switch therapy to a biosimilar medicine for a patient. In some instances, it may be appropriate to avoid switching from one biological medicine to another during a specific treatment course/period or for chronic therapies.

To avoid inappropriate substitution and ensure the proper identification of the product for pharmacovigilance monitoring, bio.be recommends that prescription for biological products, whether original or biosimilar, should always be by brand name (or invented name) and not by INN.

Such prescription rules are particularly of relevance in Belgium as the government has now required physicians to prescribe a minimum amount of prescriptions for 'cheaper products'. Failure to prescribe this minimum amount could lead to financial penalties. In its definition of 'cheaper products', the government has included all prescriptions by INN, which means that physicians get an incentive for prescribing by INN. This may also include products that are still under patent and do not have any generic equivalent or corresponding biosimilars.

Bio.be believes that in the interest of patients, prescription by INN for biological medicinal products should not be allowed in order to avoid inappropriate or inadvertent substitution. Even in the case of products under patent, it is important to prescribe by brand name in order to avoid any potential confusion between identical or very similar INNs for different products, as can be the case for biological medicines.

Making prescription by brand name mandatory in the case of biological medicines would also ensure that healthcare professionals and patients in Belgium are better informed about any potential issues relating to switching between biological medicines.

#### **5. Conclusion and bio.be recommendations**

Bio.be recommends that prescription for biological medicines should always be made by brand name and not by INN. Any decision to substitute one biotechnology medicine with another should always be made with the knowledge and explicit prior consent of the physician.

Bio.be's members would be pleased to assist and support the competent authorities as may be required to address subjects contained in the position and to work with them in developing necessary regulatory amendments.

Bio.be also supports any initiative which would foster the healthcare professionals' understanding of the specific nature of biological medicinal products and of potential issues that may be associated with product inadvertent or inappropriate substitution.



**Bio.be is the Belgian biotechnology industry organisation. Founded on January 23 2006 as a result of the merger of the Belgian Bioindustries Association (BBA) and BelgoBiotech, Bio.be represents the companies and professionals involved in research, development, testing, production or marketing of biotechnology applications, as well as those servicing the biotechnology community.**

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