Making Medicines Affordable

EGA POSITION FOLLOWING PUBLISHED CONSENSUS REPORT ON WHO INFORMAL CONSULATION WITH REGULATORS ON INN POLICY FOR BIOSMILAR MEDICINAL PRODUCTS

Introduction

It was with great interest that EGA and EGA companies took note of the recommendations to the WHO INN Expert Group put forward by the regulators during the meeting in Geneva on 3-4 September 2005 and published via the WHO consensus report.

In order to further contribute to the ongoing debate on INN allocation to biologics and biosimilar medicinal products in particular and in view of the INN ad-hoc meeting on 23-24 April 2007 in Geneva, we would like to take this opportunity to share our position regarding the regulators' recommendations.

EGA supports that

- INNs should be based, as now, on considerations of molecular characteristics and pharmacological class and that there should be no specific process introduced for naming biosimilar medicinal products.
- EGA also supports the recommendation that there should be no change in policy and no distinctive INN designation introduced to indicate a biosimilar product.
- EGA also agrees that INNs for these products should be assigned according to the standard process for naming biologicals, **BUT** that 'standard process' has to acknowledge the **concept of comparability** that is already applied to originator biological products as they go through process changes. The concept of comparability is indeed a scientific concept which applies equally to the comparability exercise for a change introduced in the manufacturing process of a given product and to the comparability exercise for a product claimed to be similar to an authorised originator product. **However it is not clear that the 'standard process' today is understood by all to include this acknowledgement of the potential to demonstrate comparability / sameness.**

It would indeed be scientifically inconsistent to ask a company to apply for a different INN for a biosimilar product, which has been proven to be comparable to an originator product (i.e. where there is no significant difference in terms of quality, safety and efficacy), while recognize at the same time that variability exists between originator products with the SAME INN or even within the same manufacturer.

As mentioned already in previous EGA position papers, current analytical technology demonstrates that:

- at the level of secondary, tertiary and glycosylation fine structure, biologic substances from a given manufacturer (recognised by a single INN) are actually a complex mixture of molecules that differ very subtly both from each other and from production run to production run.

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- It is possible to characterise a biological product manufactured by a different process and show, within the limits of this variability and analytical sensitivity, that it is the same.

Therefore, from a scientific point of view there is no reason to deny the possibility that two biological products could have the same INN on the basis of being demonstrably comparable. If proven to be comparable to a reference product, the biosimilar product should be entitled to have the same INN.

However we recognize that the degree of similarity of the biosimilar product with the reference product is critical. We therefore would like to share with you our thoughts regarding the following frequently asked question:

How close is close enough regarding the glycosylation of biosimilar recombinant proteins for therapeutic use:
Glycosylated proteins consist of mixtures of proteins with the identical amino acid sequence and different glycovariants. The glycosylation can be readily characterized if the chemical structure of each individual glycan can be determined and the quantitative composition in total and at each glycosylation site of the individual glycans can be measured. To achieve this goal, a set of orthogonal separation and identification methods is available and already applied for comparability assessments.

The criteria for the comparison of the biosimilar candidate and the reference product are based on

1. **Understanding the batch to batch variability of the reference medicinal product**

The variability of the reference product determines the acceptable range of variability of the biosimilar product. The manufacturing process for the biosimilar is systematically designed to meet the product characteristics of the reference product. Using principles of 'Quality by Design', it is already state of the art to develop a manufacturing process that delivers a glycosylated protein, which is comparable to the reference product. For example, based on the prerequisite that the glycosylation can be readily characterized, the biosimilar candidate is considered as comparable, if the variability of its glycosylation lies within the variability of the glycosylation of the reference product.

2. **Classification of the product variants into product-related substances or impurities – according to the definition provided in ICH Q6B**

In addition to the physicochemical testing, also biological and preclinical characterization is performed. If it can be demonstrated by applying such adequate biological and/or preclinical testing that a product variant, i.e. a glycovariant, can be considered to have the same efficacy profile as the main component, the variant is classified as a product related **substance**. For such a variant the comparability criteria can be set less stringent than for a variant, which differs in its efficacy profile and which is therefore classified as a product related **impurity**.

3. **Level of understanding the relevance of subtle differences on safety and efficacy according to ICH Q5E**

In the case that subtle differences in the characterization data between the biosimilar and reference product are expected, a comprehensive overview of all available information including the physicochemical, biological, preclinical and clinical data is required to justify the

comparability criteria. Only with this holistic view, the relevance of subtle differences on the final safety and efficacy profile could be determined, which allows an adequate evaluation of the overall comparability between the biosimilar and the reference product.
In conclusion, EGA continues to believe that:

- only scientifically substantiated criteria should be used to allocate INNs;
- the INN system should remain to identify the active substance and not the medicinal product;
- the purpose of the comparability exercise undertaken by developers of biosimilar medicinal products is to assess the sameness or equivalence of the biosimilar product with the reference product. A successful outcome permits the use of the same INN as that allocated to the reference product except in cases where the competent regulatory authorities may conclude otherwise in the best interest of public health;
- only the regulatory authorities — not the WHO — have the scientific expertise to decide whether or not a biosimilar product is close enough to the reference product to be entitled to carry the same INN.

Last EGA recommendations regarding a new WHO INN policy, if any

WHO should be very careful not to move towards a new policy which could end up becoming a 'double standard ruling' i.e., one for so-called regulated markets (where extensive comparability studies are required) and another one for so-called less-regulated markets (with currently no requirements for comparability data). This risk should be kept in mind as an INN application is and remains voluntary and the legal requirement to use an INN may not be that frequent in WHO member countries.
It is also worth reminding that WHO will never be in the position to control worldwide the use of the INNs by applicants and regulators because WHO cannot force a company to apply for an INN and cannot oblige the regulators to accept an INN allocated by WHO. Consequently the risk of some degree of inconsistent use of INNs is likely to continue in the future.

For truly new originator active substances, applicants are encouraged by regulators to apply for an INN as early in the development stage as possible. A WHO procedure which provides more guidance regarding the timing of an INN application for a new originator active substance during its development phase as well as guidance regarding the minimum documentation to be submitted at the time of INN application would also reduce the risk of possible inconsistencies.

Last but not least, it is crucial that the new WHO INN policy, if any, does not introduce new inconsistencies in the respective market places. A balance has to be struck between non retroactive implementation of any new INN policy and possible introduction of new inconsistencies.
In any case, the EGA is confident that science will drive the process.

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