Process on Corporate Responsibility in the field of Pharmaceuticals
Platform on Access to Medicines in Europe

Project Group on Market Access and Uptake of Biosimilars
Work Area G: "Develop information material directed to healthcare professionals"

1. INTRODUCTION

The Standing Committee of European Doctors (CPME) recognises the potential development of biosimilars in the European market. So far the pricing of biosimilars has been, admittedly, lower than the original biopharmaceutical, but not enough. This is probably one of the reasons why substitution (whether primary or secondary) [1] schemes have probably not been cost-efficient enough to warrant wide support.

For the medical professionals the key issue is to ensure that biosimilars are at least as effective, safe and of good quality as the original reference biopharmaceuticals. Therefore, CPME calls upon the Commission to ensure that the following concerns are taken into account into any future regulatory and non-regulatory action regarding biosimilars:

1. Clinical efficiency and safety: biosimilars are a collection of large, complex and heterogeneous proteins which are very sensitive to changes during the manufacturing process of the compounds, transport and storage. Minor changes may have a significant impact on the quality, purity, biological properties, clinical activity and safety of these compounds. Quality assurance assays for biopharmaceuticals and biosimilars are considered to be less precise than those for small-molecule drugs.
2. Secondary substitution is critical with biosimilars for the reasons mentioned above. Secondary substitution must be acceptable only on a case by case basis. Moreover, the naming and other means used for identifying biosimilars must be thoroughly standardised to avoid confusion and accidental substitution between biopharmaceuticals and their biosimilars and vice-versa.
3. Post-marketing surveillance: It is of utmost importance to apply the strictest monitoring in order to minimise the possible occurrence of side-effects after the launch of the product.

[1] "Substitution of an original biopharmaceutical for a biosimilar can be either primary or secondary. Primary substitution is defined by the use of a biosimilar rather than its original when starting a treatment. Secondary substitution is defined by the replacement of an original drug by a biosimilar already in use in a patient"

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2. THE MAIN CONCERNS OF MEDICAL DOCTORS REGARDING BIOSIMILARS

Advantages of biosimilars: similar efficacy at a lower cost than that of the reference products.

Disadvantages: biosimilars can never be identical to the reference original product. This can lead to problems such as the risk of immunogenicity or of unexpected adverse reactions. It is well known that the administration of foreign proteins can enhance the risk for the development of antidrug antibodies (ADA).
Numerous factors such as the disease state, drug-related factors (product-and process related factors), patient-related factors (age, sex, genetic background, etc.) and treatment-related factors (concomitant drugs, route of administration, etc.) are able to influence the immunogenicity, the pharmacokinetics and tolerability of biosimilars. It is therefore more difficult, but at the same time more important to be able to rely on pre-clinical and clinical comparability studies between the biosimilars and their corresponding innovator products.

CPME recognises the benefits of those biosimilars that have been proven to have similar efficacy as their respective reference medicines at a lower cost. Every measure aimed at increasing the number of prescriptions of biosimilars by European physicians should ensure that the key concerns for the doctors, i.e. safety of the treatment and its efficacy are as close as possible to their respective reference medicines.

3. PROPOSED MEASURES TO INCREASE ACCEPTANCE BY THE MEDICAL DOCTORS

1. Develop a reliable and systemised source of information with an index of all innovator biopharmaceutical products and biosimilars that would include continued updated information on pharmacokinetics and immunogenicity, with interchangeability studies as they become more widely accessible. This information tool would need to be easily accessible to all European physicians (i.e. online) and handled by an independent authority (e.g. the European Medicines Agency - EMA)[2]
2. Develop clear information material about the existing guidelines for market approval of biosimilars. CPME is well aware of the guidelines issued by the EMA's Committees for Medicinal Products for Human Use (CHMP) which describe in detail the requirements for market approval. Enforcement of these guidelines should be ensured to the highest standards across the EU market, regardless if the biosimilar is produced in the EU or imported from outside the European market.
3. Develop information material on the traceability of the manufacturing process of the biosimilar (from manufacturing to dispensing). This measure should help addressing the safety concerns mentioned in the introductory remarks about the biosimilar sensitivity to changes during the manufacturing, transport and storage, particularly when the biosimilar has been imported from abroad the EU area.

[2] The online information database on biosimilars could include a search engine allowing looking for either specific name search and/or broadening from indication and original substance. It should contain the following information (non-exhaustive list): adverse react information, contact information on the producer and link to other papers with relevant related information.

4. Accept secondary substitution only on a case by case basis with special attention to the individual patients risk/benefit balance. Primary substitution is more widely acceptable as long as the biosimilar has the same indication. The prescriber has to be notified so the patient's chart has, in a clear and unquestionable manner, the correct name of the product whether the original or the biosimilar.

CPME is aware that the scope of the 'Project Group on Market Access and Uptake of Biosimilars' is limited to the adoption of non-legislative measures. While acknowledging this particular scope of the project, CPME would like to invite the European Commission to consider action at regulatory level, which could further increase the trust and acceptability of biosimilars by European physicians, namely:

1. Adoption of strict standardisation rules concerning the names given to the product in order to avoid confusion and unintentional substitution.
2. Development of improved assays for the detection of antidrug bodies (both IgM and igG classes), and particularly cell-based assays for the detection of neutralising antibodies and screening for antidrug bodies.

Furthermore, CPME recalls the importance to implement to the highest standards the existing legislation on Pharmacovigilance, particularly as regards biosimilars. Post marketing surveillance of biosimilars is of utmost importance in order to identify, assess and minimise the short, medium and long-term risks with special attention at the possible occurrence of side effects, and screening for antidrug bodies.

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BIBLIOGRAPHY

1. **Biosimilars: pharmacovigilance and risk management**
Source: Pharmacoepidemiol Drug Saf. 2010 Jul; 19(7):661-9.
By Zuñiga L, Calvo B,

2. **Statistical assessment of biosimilar products**
Source: J Biopharm Stat. 2010 Jan; 20(1):10-30.
By Chow SC, Liu JP.

3. **Worldwide experience with biosimilar development**
Source: Landes Bioscience Volume 3, Issue 2 March/April 2011Pages 209 - 217
McCamish M, Woollett G.

4. **Biosimilars: controversies as illustrated by rhGH**
Source: Curr Med Res Opin. 2010 May; 26(5):1219-29.
By Declerck PJ, Darendeliler F, Góth M, Kolouskova S, Micle I, Noordam C, Peterkova V, Volevodz NN, Zapletalová J, Ranke MB.

5. **Statistical assessment of biosimilar products**
Source: J Biopharm Stat. 2010 Jan; 20(1):10-30.
By Chow SC, Liu JP.

6. **Biosimilars 2.0: guiding principles for a global "patients first" standard**
Source: Landes Bioscience Volume 3, Issue 3 May/June 2011Pages 318 - 325
By Miletich J, Eich G, Grampp G, Mounho B.

7. **Recommendations and requirements for the design of bioanalytical testing used in comparability studies for biosimilar drug development**
Source: Bioanalysis. 2011 Mar; 3(5):535-40.
By Cai XY, Gouty D, Baughman S, Ramakrishnan M, Cullen C.

8. **Biosimilar medicines--new challenges for a new class of medicine**
Source: J Biopharm Stat. 2010 Jan; 20(1):3-9.
By Fox A.

9. **Biosimilars: policy, clinical, and regulatory considerations**
Source: Am J Health Syst Pharm. 2008 Jul 15; 65(14 Suppl 6):S2-8.
By Gottlieb S.

10. **Biosimilar therapeutics-what do we need to consider?**
Source: NDT Plus. 2009 Jan; 2(Suppl_1):i27-i36.
By Schellekens H.

11. **Follow-on biologics: challenges of the "next generation"**
Source: Nephrol Dial Transplant. 2005 May; 20 Suppl 4:iv31-36.

By Schellekens H.

12. **Biosimilar epoetins: an analysis based on recently implemented European medicines evaluation agency guidelines on comparability of biopharmaceutical proteins**
Source: Pharmacotherapy. 2005 Jul; 25(7):954-62.
By Combe C, Tredree RL, Schellekens H.

13. **Biosimilar epoetins and other "follow-on" biologics: update on the European experiences**
Source: Am J Hematol. 2010 Oct; 85(10):771-80.
By Jelkmann W.

14. **Biosimilars: it's not as simple as cost alone**
Source: J Clin Pharm Ther. 2008 Oct; 33(5):459-64.
By Roger SD, Goldsmith D.

15. **Biosimilars: how similar or dissimilar are they?**
Source: Nephrology (Carlton). 2006 Aug; 11(4):341-6.
By Roger SD.

16. **Immunogenicity of biotherapeutics in the context of developing biosimilars and biobetters**
Source: Drug discovery today Volume 16, Issues 7-8, April 2011, Pages 345-353
Barbosa MD.

17. **The regulatory framework of biosimilars in the European Union**
Source: Drug Discov Today. 2011 Aug 12. [Epub ahead of print]
Minghetti P, Rocco P, Cilurzo F, Del Vecchio L, Locatelli F.

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