International Journal of Risk & Safety in Medicine 21 (2009) 105–109
DOI 10.3233/JRS-2009-0460
IOS Press

Appendix 1

How the European Union reviews and approves 'follow-on biologics' or biosimilar products [1]

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Mr. Chairman,
Honourable Members of the HELP Committee,

Thank you for giving me the opportunity to testify today. My name is Nicolas Rossignol. Since 2003 I have been working as an Administrator within the European Commission, in the division in charge of the European Community pharmaceutical legislation. The European Commission has three main roles in the area of pharmaceuticals: it proposes new legislation; it implements existing legislation; and it authorises and monitors the placing on the EU market of certain types of medicines, including all biotech products produced by recombinant DNA technology (e.g. insulin, growth hormones, etc.). The granting of this 'marketing authorisation' is done on the basis of a scientific evaluation of the product, which is carried out by the European Medicines Agency (EMEA).

Since 2003 I have been responsible within the European Commission for the implementation of the EU Pharmaceutical legislation in the specific field of 'follow-on biologics', which we call in Europe 'similar biological medicinal products' or 'biosimilars'. I have been involved in the legal, regulatory and scientific aspects of this topic. It is arguably one of the most complex issues that the European Community has faced in the area of pharmaceuticals in the last 5 years.

My testimony today will focus on how the European Union reviews and approves 'follow-on biologics' or biosimilar products. I will address the following issues:

- How and on which principles is the EU legal framework for biosimilars established?
- What regulatory and scientific work has been achieved in the EU since the establishment of this framework?
- What has been the EU practical experience so far with the regulatory environment on biosimilars, and what are the challenges?

[1] Testimony before the U.S. Senate Committee on Health, Education, Labor and Pensions during the hearing on the important question of whether Congress should give FDA the authority to approve follow-on versions of biologic medicines, 8 March 2007. Available at http://help.senate.gov/Hearings/2007_03_08/Rossignol.pdf, accessed January 6, 2009. Republished with permission of the author.

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1. How and on which principles is the EU legal framework for biosimilars established?

The notion of 'biosimilar product' or 'biosimilarity' has been introduced in EU legislation in June 2003 [5], and further elaborated with the adoption of the EU 'Pharmaceutical Review' in April 2004 [1]. This notion allows a manufacturer to submit an application and get an authorisation for a product claimed to be similar to another biological medicine – the 'reference product'. The rationale for creating this new licensing route is that biologics similar to a reference product "do not usually meet all the conditions to be considered as a generic" [4]. Although the EU 'generic' route remains legally open to biologics (the word 'usually' implies that in some cases, generic provisions might be sufficient), this is more a theoretical possibility than a practical way forward given the current state of science. It is clear for EU regulators today that the complexity of biological molecules, the fact that they are produced in living organisms and their sensitivity to changes in the manufacturing process make it virtually impossible for applicants to produce an identical copy of a reference biological product. In other words, the licensing route for biosimilars is based on the principles that:

- biologics are not chemical drugs;
- the generic approach is, in the quasi-totality of cases today, very unlikely to be applicable to biologics: biosimilars are not 'biogenerics'.

The regulatory framework for biosimilars is therefore the only one licensing route to be applied to biologics claimed to be similar to a reference product. Three main eligibility criteria can be spelled out:

First, the product must – obviously – be a biological medicine. In legal terms, this means that any type of biologic could be licensed as a biosimilar, including complex biologics such as blood-derived products, vaccines, gene/cell therapy products, etc. However, the approach is for scientific reasons more likely to be successful today for products which can be thoroughly characterised, such as proteins produced by recombinant DNA technology (e.g. insulin, growth hormones). Conversely, it is more difficult to apply to other types of biologics which by their nature are more complex (e.g. vaccines), or to those for which little regulatory experience has been gained so far (e.g. gene therapy).

Secondly, the reference product must have been authorised within the European Community. Importantly, it is not legally required that the reference product is still authorised at the time the biosimilar application is filed.

Thirdly, the application has to be submitted after the expiry of data exclusivity. In the EU, innovative products benefit from a data exclusivity period, which currently varies from six to ten years for old products, and which has been recently harmonised to the so-called '$8 + 2 + 1$' period. This means that an authorised product will get a data exclusivity period of eight years, after – and only after – which a company will be allowed to submit a biosimilar application. However, the actual placing on the market of the biosimilar will not be permitted until ten years (i.e. $8 + 2$) have elapsed from the initial authorisation of the reference product. In addition, the period will be extended to a maximum of eleven years (i.e. $8+2+1$) if, during the first eight years of data exclusivity, the holder of the reference product obtains an authorisation for new therapeutic indication(s) which bring(s) significant clinical benefit in comparison with existing therapies. This balanced approach has been favoured in order to reward companies who develop innovative products, without impairing the development of the generics and biosimilar industry.

As regards the kind of data required to file a biosimilar application, the EU legislation is based on the principle that a 'one size fits all' approach is unworkable in this area. The type and amount of pre-clinical and clinical data are not predefined in legislation but are determined on a case by case basis, on the basis of the relevant scientific guidelines. This approach reflects the wide spectrum of molecular complexity among the various products concerned, ranging from relatively simple molecules such as insulin to

far more complex ones. Thus, the requirements to demonstrate safety and efficacy of a biosimilar are essentially product class-specific. In theory, a biosimilar application could therefore range from being almost 'as abridged' as a generic application (with very limited non-clinical/clinical studies), to being nearly as complete as a full, stand-alone application. The task to determine this range as precisely as possible, concretely and on a scientific basis, i.e. by taking in consideration the characteristics of the concerned products, has been put in the hands of the European Medicines Agency (EMEA), to which the EU legislators have given a mandate to issue scientific guidance.

2. What regulatory and scientific work has been achieved in the EU since the establishment of this framework?

The first EMEA guideline on biosimilars was released for consultation in November 2004 [2]. This was a general, 'overarching' guideline designed to introduce the concept of biosimilarity in scientific terms. Since then, a number of guidelines have been issued, most notably on:

- general quality aspects;
- general pre-clinical and clinical aspects;
- product-class-specific pre-clinical and clinical aspects on insulins, growth hormones, erythropoietins and granulocyte-colony stimulating factors;
- immunogenicity of biotechnology-derived therapeutic proteins.

All these guidelines relate to molecules which can be thoroughly characterised with state-of the-art analytical methods and for which extensive regulatory experience is available.

From a legal perspective, it is not necessary that EMEA issues guidance in one area to enable manufacturers to submit applications. Besides, EMEA guidelines are usually not legally binding – alternative approaches which depart from available guidelines, if properly justified by the manufacturer, may also be accepted. In the case of biosimilars, however, the legislation makes explicit reference to compliance with the detailed guidelines to be issued by the EMEA.

Without going into the scientific details of these guidelines, one important underlying principle is worth being mentioned: to substantiate its claim of biosimilarity, a manufacturer must conduct a direct and extensive comparability exercise between its product and the reference product, in order to demonstrate that the two products have a similar profile in terms of quality, safety and efficacy. Only one reference product is allowed throughout this exercise. Approaches using indirect comparisons (i.e. through other products) are unlikely to be successful from a scientific viewpoint.

The EMEA guidelines make it clear that it is not expected that the quality attributes (e.g. the molecular structure) in the biosimilar and the reference product should be identical. Actually, minor structural differences are reasonably expected given the very nature of biologics and the inherent variability in the way they are produced. However, those differences should in any event be justified on scientific grounds and would be considered on a case-by-case basis, in relation to their potential impact on safety and efficacy. The underlying scientific assumption is that differences between the biosimilar and the reference product are, *a priori*, regarded as having a potential impact on the safety/efficacy profile of the product. They will therefore influence the type and amount of data required by the regulators in order to make a satisfactory judgment of compliance with EU standards. For example, changes in glycosylation patterns are well known for having potential effects on the safety/efficacy profile of glycosylated proteins.

In case the reference product has more than one therapeutic indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for

each of the claimed indications. In certain cases it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product, but this is not automatic (it may also be that the biosimilar applicant does not claim all the therapeutic indications of the reference product). Justification will depend on a number of factors, such as clinical experience, available literature data, etc. In essence, regulators' judgement to approve therapeutic extrapolation is again product specific.

3. What has been the EU practical experience so far with the regulatory environment on biosimilars, and what are the challenges?

The EU framework on biosimilars is relatively new. Two products have been authorised so far under this frameworkv: the first is the growth hormone Omnitrope, which was authorised by the European Commission in April 2006 [6]. A second growth hormone, Valtropin, was also authorised in April 2006. One product (Alpheon, an interferon) was given a negative scientific opinion by the EMEA in June 2006 [3]. One of the main reasons for this is that the EMEA had major concerns regarding the comparability of Alpheon and its reference product (Roferon-A), because of differences identified between the two medicines, such as impurities. The EMEA was hence of the opinion that Alpheon could not be considered as a biosimilar. A number of additional applications are already in the pipeline at the EMEA. They mainly concern erythropoietins (EPOs), interferons, insulins and granulocyte-colony stimulating factors (G-CSFs). An early dialogue between the manufacturers, the EMEA and the European Commission has proven critical to sort out the various regulatory and scientific issues that applicants may face.

Open debate with all stakeholders has proven extremely useful to gather input, compare experience and build consensus, in particular when drafting guidance documents. As science evolves, our ability to better characterize biologics should increase, as well as our regulatory experience with these products. One can therefore expect, in the long term, that the 'range of possibilities' (types of biologics for which the biosimilar approach is scientifically acceptable, amount of clinical data required to demonstrate biosimilarity, etc.) will become more and more precise.

The 'legal construction' of the European Community assigns certain competences to the European Commission, while some others are for the Member States. The issue of pricing and reimbursement, in particular, is basically of national competence in Europe. Therefore the EU harmonised regulatory framework on biosimilars does not address this issue. Given the limited number of products authorised so far and the fact that this framework is quite new, it is probably too premature to assess the actual impact of the introduction of biosimilar products on the price of biologics in Europe. However, this is a parameter the European Commission is likely to monitor with particular attention in the coming years.

Some new issues have fuelled the EU debate on biosimilars in the recent past. One of them relates to interchangeability between biosimilars and innovative products. It is important to bear in mind that the EU regulatory framework on biosimilars is designed to achieve one objective: to assess the quality, safety and efficacy of biosimilars so that these products comply with the same EU health standards as any other medicine. This framework, however, is not legally designed to evaluate whether a biosimilar is actually interchangeable in medical practice with the reference product, i.e. whether one product can be safely substituted for the other and have the same biologic response without triggering adverse reactions.

Interchangeability is also beyond the scope of the existing EMEA guidelines on biosimilars. Finally, one last point in discussion today relates to the naming of biosimilars. Medicines usually have an International Non-proprietary Name (INN) (e.g. 'insulin') which is defined by the World Health Organisation. Generics usually have the same INN as the reference product, and healthcare professionals often

prescribe by INN. The biosimilar industry has been advocating that a biosimilar product, once proved biosimilar, should be entitled to have the same INN as its reference product. On the other hand, the innovative industry has claimed that a distinct INN should be assigned to biosimilars, in particular for the sake of traceability and pharmacovigilance. Our understanding within the European Commission and EMEA is that the rules of the INN naming system should remain international, science-based rules. The same scientific rules should apply to all products, be they innovative products or biosimilars. The INN nomenclature should not be used as a way to distinguish between biosimilars and other types of products.

4. Conclusion

Overall, I believe it is fair to say that the flexibility of the EU regulatory framework on biosimilars has been positively welcomed by both sides of the pharmaceutical industry. The fact that the legal basis is relatively concise and focuses on the key legislative elements of this framework, while technical aspects are addressed through guidelines, has enabled us to undertake a cautious and balanced, 'not too stringent, not too loose' approach to allow biosimilar manufacturers to get streamlined access to market, without compromising public health. The defining principles which have guided us so far in regulating biosimilars will remain crucial to address the challenges still ahead of us. Our primary objective should remain to protect public health: biosimilars should meet the same standards of quality, safety and efficacy as any other biological product in the EU. Our regulatory framework should remain based on science: it should fully take account of the fact that biologics are, in the vast majority of cases, not simple molecules. And finally, our experience over the past few years demonstrates, I believe, that transparent and open dialogue with all sides of the industry is key to put in place a robust and adapted regulatory framework in this emerging field.

Thank you.

Disclaimer

The views expressed in this Testimony are purely those of the witness and should not be regarded as stating an official position of the European Commission.

References

[1] Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, *Official Journal of the European Union* L136, 30/4/2004, pp. 0034–0057.
[2] http://www.emea.europa.eu; A guideline on pre-clinical and clinical issues related to a biological substance of extractive origin (Low Molecular Weight Heparins), in preparation.
[3] http://www.emea.europa.eu/pdfs/human/opinion/19089606en.pdf.
[4] Recital (15) of Directive 2004/27/EC (see [1]).
[5] Section 4, Part II, Annex I to Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, as amended by Commission Directive 2003/63/EC of 25 June 2003, *Official Journal of the European Union* L159, 27/6/2003, pp. 0046–0094.
[6] The register of medicinal products for human use authorised by the Commission, available at: http://ec.europa.eu/enterprise/pharmaceuticals/register/alfregister.htm.