



*Making Medicines Affordable*

Brussels, 4 December 2006

**Albert van der Zeijden**  
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Dear Mr van der Zeijden,

**Re: IAPO Briefing Paper on Biosimilar Medicines**

On behalf of the Biotechnology and Biosimilar Medicines Committee of the European Generic Medicines Association, I would like to comment on the recently published IAPO Briefing Paper on Biosimilar Medicines.

We welcome the attempts of IAPO to provide information to patients on biosimilar medicines and have appreciated the opportunity to contribute to the research and to comment on early drafts of the Briefing Paper. However important remarks from EGA and EGA companies have not been taken into account and we are concerned by a number of comments made in the briefing paper which we believe provide an inaccurate picture of biosimilar medicines for patients. Our primary concerns are detailed below.

1. Sections 4.2.1 and 4.2.2 on pages 15-16 contain analogies and some misinterpretations that we believe will misinform and mislead patients. These should be corrected.
  - a. The 'two cooks' analogy is flawed, inappropriate, and portrays a very major misunderstanding of the science of biosimilar medicines. This is particularly concerning since it appears in a part of the report which is supposed to be independent in its approach. The analogy ignores the fact that biosimilars are actually designed to match a reference product, and that the whole purpose of process by design and validation of production methods is to guard against exactly the scenario postulated by the example, ie, two manufacturers making a product differently.

The correct version of the 'two cooks' analogy is that of a head chef in an exclusive restaurant chain working with various qualified chefs in each chain to ensure that, irrespective of the shift, the presence or not of the head chef, or the actual kitchen being used, that the dishes are the same in look and taste every day. (In such an analogy the EMEA could be considered the head chef, and the individual restaurants as individual companies producing different biosimilars, or the originator products).



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If the analogy is to focus on variability, then it must focus on the variation in dishes made by the same chef in the same kitchen to the same recipe on different days - reflecting the batch-to-batch variability in the originator product.

- b. The statement on page 16 that analytical testing technology is not sufficiently advanced to assure that biosimilars are the same as the original product does not go on to say that this is the reason clinical trials are conducted for approval of biosimilars. Analytical technology will prove that, within the known variability of the originator product, the biosimilar is the same (ie, has no greater variability) across a wide range of parameters. The clinical program then confirms that any undetected variances are not clinically/therapeutically relevant. Once again, the role of the regulators in policing and monitoring 'sameness' has been downplayed. Table 3 on page 19 also makes this suggestion when it says biosimilars cannot be identical. This downplays the fact that the originator product is itself variable. Consequently, the paper fails to give patients the full story and thereby introduces unjustified doubts about the approval system.
  
  - c. The section 4.2.2 would appear to be an attempt to articulate patient specific risks of biosimilars. However there is no balanced discussion of what those risks are and how the regulatory standards seek to address them. Five points are made of which four have no relevance what-so-ever to any potential difference in performance between a biosimilar and the originator product to which it has been compared. The fifth risk applies to both biosimilar and reference products.
    1. Higher risk of immunogenicity with biologic medicines is a function of biologic medicines, not of biosimilars per se.
    2. Variability in patient response is a function of the active drug, not the manufacturer. Here, the whole approval process is designed to ensure biosimilars have the same therapeutic effect (including response and adverse event rate) as the originator.
    3. Changes in manufacturing processes that can result in small differences that affect response rates and adverse events such as immunogenicity is the only point made where valid distinctions can be made between biosimilars and the original product. As they are made by different manufacturers and processes, there is a finite risk of differences in performance. However, as the PRCA/Eprex<sup>®</sup> case demonstrates, this is just as much an issue when the original manufacturer changes their process or site of manufacture.
    4. Unpredictability of immunogenicity is a concern, but the linkage of this specific issue with biosimilars alone is difficult to understand.
    5. All medicines are clearly labelled to allow traceability. In Europe for example, the vial or syringe will contain the product name, INN name, manufacturer's name, marketing authorisation number, batch number and in some cases a unique regulatory code. Moreover, biosimilar medicines in the EU will not for example be allowed to market with INN alone. EU biosimilar medicines will have to be linked to the company name or to a product brand which provides identification of products for healthcare professionals and patients.
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2. The comments by the Genetic Interest Group on page 33 under ‘biosimilars and targeted therapy’ are very concerning. They highlight the need for this report in the first place, but they also highlight some of its shortcomings. The statements that ‘biosimilars offer the potential for targeted therapy’, that ‘biosimilars should not always be seen as always having lower efficacy than the original’ and that ‘some biosimilars may be more effective in certain types of patients than the original innovator drug’ are factually incorrect and deserve editorial comment and correction. The whole basis of approval for a biosimilar is that it has comparable and therapeutically equivalent efficacy and safety to the reference originator product (It will also be analytically comparable). Biosimilar medicines will never be less effective, as they would not be approved in the first place unless studies showed they were clinically the same. Any statement to the contrary is a myth promulgated by vested interests desiring to see biosimilars fail. Equally, there could not be studies to show differing specific efficacy in specific sub-groups in the approval of a biosimilar. Such studies, if conducted, would disallow the biosimilar from being a comparable product to the originator and so would require a different legal basis of approval.
3. The Eprex case history on page 52 also contains at least one factual inaccuracy and one major omission that we believe is particularly relevant in understanding the significance of PRCA.
  - a. The statement that ‘no differences were identified using currently available and state-of-the art analytical technology’ is incorrect. Janssen Cilag, the manufacturer of the product, have published data themselves showing analytical differences between the product causing increased incidence of PRCA and the product after that period.<sup>1</sup>
  - b. The paragraph on the incidence of the PRCA misleadingly suggests that the incidence of PRCA is high and limited to one product. In fact there is a baseline incidence of PRCA that all patients experience. The increase in PRCA observed with Eprex<sup>®</sup> was a significant multiple of the baseline, but still remained at a very low level (~40-50:100,000 according to at least one source<sup>2</sup>).
4. In the Executive Summary, IAPO acknowledge that a regulatory pathway exists in Europe for biosimilars “to guarantee their safety, quality and efficacy”, yet the role of the regulatory authorities in ensuring the quality of medicines seems to be ignored elsewhere in the paper where doubts are raised about the quality of biosimilars.

In general the paper seems to imply that patients should be seriously concerned about the complexity of these medicines merely because they are biosimilars. In fact the real basis of concern should, where appropriate, be due to their nature as biologics - and such concerns apply equally to originator products as well as to biosimilars.

- a. Table 2 on page 15 reinforces this view. For example, the comment that it is harder to predict in the lab what will happen in the patient flies in the face of much higher success rates in late stage clinical trials for biologics over drugs. The comment about stability ignores the fact that many drugs are highly unstable, requiring the same 2-8 degree refrigeration as many biologics and, in

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<sup>1</sup> Epoetin-associated pure red cell aplasia in patients with chronic kidney disease : solving the mystery. Katia Boven, John Knight, Fred Bader, Jérôme Rossert, Kai-Uwe Eckardt and Nicole Casadevall. Nephrology Dialysis Transplantation (2005) 20 (Suppl 3)

<sup>2</sup> Pure Red-Cell Aplasia and Epoetin Therapy, The New England Journal of Medicine September 30, 2004

many cases, can only be made available in powder form due to the instability of solutions.

- b. Section 4.3 also, because of its weight, implies that biosimilar medicines have different safety and efficacy concerns that need to be addressed in patient information. Yet the concerns listed apply to all medicines. After all, decisions about the use of, safety of, inter-changeability of and substitution of medicines – including biosimilars – are made by regulators, government substitution authorities or specialised care formularies (in most cases for biologics). Once this safety determination is made, should a patient really be concerned about which version of a medicine with a given INN name (e.g. a biosimilar EPO-alpha) they are receiving? We are interested in understanding the views of patients on this topic, but in the absence of solid scientific evidence or any other rationale, we are very concerned about any policy that biases patients for or against a particular source of the same medicine when regulatory authorities have already assessed this potential concern. The issues associated with promoting one active substance against another (and the patient information needs that go with that) are totally different to the issues that are faced by generics/biosimilars versus the originator of the same active substance.

5. The remaining comments are less material, but still require comment.

- a. At several points in the paper, IAPO argue that the cost savings for biosimilar medicines are unknown. This begins in the Executive Summary and is repeated on page 13. We would point out that the initial pricing approvals for Omnitrope<sup>®</sup> have been in the range of 20-30% below the list price of the reference product ... and that 30% cost savings on biosimilars equate to very large numbers in euro and/or in terms of additional access to treatment (€2-3b per year on just five products in Europe). It is thus already clear that biosimilars will result in real price savings for patients and providers.
- b. In table 3 on page 19 the statement that biosimilars must have ‘very high and robust standards of manufacture’ when placed next to a statement about generic medicines that must be ‘manufactured under the same strict standards of GMP regulations required for the original medicine’ implies that biosimilar manufacturers may not comply with GMP. The fact is that GMP standards for biologics apply to all manufacturers, originator and biosimilar companies and these standards are already ‘very high and robust’ precisely to ensure integrity of the product.
- c. The comments on interchangeability in section 4.5 imply that governments and insurers will pressure clinicians to switch to biosimilar medicines to save money. However, in the context of increasing access to medicine for the entire population, it is now well established that physicians should be aware of the cost implications of their prescribing practices. Experience with generic medicines shows that the absence of such incentives and mechanisms hampers a health system’s ability to realise cost savings and in turn prevents wider access to medicines or proper allocation of limited resources. The issue is not one of placing pressure, but of ensuring that doctors become engaged in a health partnership which ensures the best use of resources whilst maintaining the same high level of quality, safety and efficacy of medicines as assured by the approval



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and registration system. Similar ‘allegations’ are made of the pressure medical practitioners may experience in section 4.6. However, it must be stressed in this context, that most biologics are administered in specialised care settings where drug therapy is governed by centre policy and formulary decisions, not by the prescribing behaviour of individual clinicians.

In conclusion we wish to stress that biosimilar medicines provide a major opportunity to greatly increase the access of safe, effective and quality pharmaceutical care to patients. We stress that biosimilar medicines will never be less (nor more) effective than the originator products since they would not be approved unless studies showed they were clinically the same. Biosimilar medicines are specifically designed to match the reference product with regards to quality, safety and efficacy and they are medicines approved according to strict European requirements as defined in the regulatory framework established in Europe for biosimilar medicines.

In this context it should be noted that true biosimilar medicines should not be confused with generic versions of some biological products which have been marketed in some countries outside the EU without the careful comparability assessment required by the EU biosimilar regulations. The rules developed and applied by the European Union are based on a strict scientific approach, which insure the highest standard of patient safety.

Yours sincerely

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European Generic medicines Association



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