

Biosimilars for Healthcare Professionals
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The EU regulatory approach to generics and biosimilars is essentially similar

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Notwithstanding the scientific and regulatory differences between generic and biosimilar medicines, the European Medicines Agency/Committee for Medicinal Products for Human Use has consistently applied a 'same active substance' approach to both.

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It is often stated that biosimilars are 'similar but not identical' to their reference product, or more generally, that two biological medicinal products cannot be identical [1, 2]. Although this statement may be correct from a purely scientific – especially biochemical – viewpoint, it is not correct from a regulatory point of view.

The European legal definition of a biosimilar is convoluted. Article 10.4 of the Directive 2001/83/EC [3] does not give a straightforward definition, but states: 'Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided.'

This legal article mainly describes what a biosimilar is not (it is not a generic), and that 'appropriate results of tests and trials' must be submitted; however, a clear definition is not provided. The legal definition of a biosimilar is somehow dependent on the legal definition of a generic, which requires a generic to have the same qualitative and quantitative composition in

active substances, the same pharmaceutical form, and being bioequivalent with the reference product.

In actual regulatory decision-making, a biosimilar has the 'same active substance' as its reference product. As we will argue below, the actual decisions from European Union (EU) regulators demonstrate that this requirement applies to both generics and biosimilars.

It is important to realize that in this context 'sameness' is not a scientific concept. Two products will never be 'the same' or identical, if one looks hard enough for differences. This also applies to generics, especially when the source of the drug substance is different. If state-of-the-art physicochemical analysis techniques are employed, some (minute) difference(s) in product-related substances/impurities will always be found. Based on such differences a well-equipped analytical laboratory will be able to differentiate between common painkillers with the same active substance, but from different sources.

Sameness is a regulatory concept; it implies that the two products contain the same active substance within the meaning of the Directive. This legal sameness has real-world implications.

Firstly, it means that the active substance in the two products must comply with the same monograph of the *European Pharmacopoeia*



or another pharmacopoeia, if such a monograph exists. Compendial monographs will use the International Nonproprietary Name (INN) as the identifier if an INN is available. Finally, neither a generic nor a biosimilar may contain a new active substance; because this would violate the regulatory and compendial principles outlined above. The regulatory system is internally consistent in this respect.

The second consequence of regulatory sameness is that no clinically meaningful differences exist between two products. Although this is not explicitly stated, it is the cornerstone of the generic/biosimilar approach: because, if a product is generic/biosimilar to the originator[†], clinical data can be extrapolated and their (clinical) benefit–risk is the same.

Recent US regulations for biosimilars state this clinical aspect more explicitly: *Biosimilarity means that the biological product is highly similar to the US-licensed reference biological product notwithstanding minor differences in clinically inactive components; and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product* [4].

Although EU regulators have not explicitly written down in the guidance that a biosimilar must have the 'same qualitative and quantitative composition in active substances' as the reference product, this principle is consistently used in regulatory decision-making. Available EU guidance is consistent with this requirement: more importantly, it is systematically applied in practice. This is exemplified by the EPAR (European public assessment report) 'Summary for the public' for the first biosimilar,

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Omnitrope (somatropin), which unequivocally states that the approved biosimilar has the same active substance as its reference product [5].

For somatropin and other non-glycosylated proteins the situation is basically the same as for generics: the active substance is the same and small differences are only observed in the excipients and product-related substances/impurities.

For glycosylated proteins, there will be batch-to-batch variability in the percentages of the different glycosylated forms, both within reference and biosimilar products. An active substance can be deemed 'the same' from a regulatory point of view, if this variability in glycosylation pattern is the same, i.e. if the glycosylation patterns have been overlapping. As a consequence, the two active substances are expected to have the same INN, because the aim of the INN system has been to provide health professionals with a unique and universally available designated name to identify each pharmaceutical substance [6]. If two active substances are the same, from a regulatory point of view, then the INNs will have to be the same. We note that the INN system may contain rare inconsistencies in this respect, due to the use of the Greek letter suffix to differentiate glycosylation patterns. For example, Retacrit (epoetin-zeta) is deemed biosimilar to Eprex (epoetin-alfa)[‡]. We feel that such inconsistencies, whilst sometimes unavoidable, should not be promoted by the liberal use of these suffixes. In this respect, we feel that the currently proposed addition of Biological Qualifiers (BQs) to the INN may obfuscate the original intention of the INN. This additional BQ suffix overlaps with the trade name and may be misinterpreted as meaning that the active substance is not the same [7].

Two reasons seem to cause that the 'same active substance' requirement is neither recognized nor correctly understood. First, as discussed above, the difference between the scientific and regulatory meaning of 'same' is not always appreciated. Second, the terms active substance and the drug substance, which have overlapping but different meanings, are sometimes mixed.

The European legal definition of generic uses the term active substance in the sense of 'active ingredient with pharmacological

activity', in line with the definition of active substance in the *European Pharmacopoeia* [8]. On the other hand, drug substance is bulk material that *can be composed of the desired product, product-related substances, and product- and process-related impurities* [9].

To put it more illustrative: the active ingredient somatropin refers to a 191 amino acid protein, which can bind to a specific receptor. The drug substance somatropin may also refer to a stainless steel drum containing a frozen aqueous solution, of which the protein somatropin is actually only a few per cent by weight[‡]. The concept of active substance has in decision-making for biosimilar unambiguously been used referring to the active ingredient and not to the drug substance.

In conclusion, European regulators have applied a consistent policy regarding assessment and approval of biosimilars. The cornerstone of this policy is that the active substance of a biosimilar must be 'the same' from a regulatory and clinical viewpoint, and should display 'no relevant differences' from a scientific viewpoint. We feel that it is important to communicate this message clearly to all stakeholders.

Author's note

[†]In pre-2004 legal language such a product would be essentially similar to the originator.

[‡]The EPAR of this specific product states that the active substance is similar, which does not reflect any scientifically relevant difference in glycosylation pattern, but only the difference in INN-suffix.

[§]Further confusion is added due to the everyday usage of the term 'API manufacturers'; these should be called 'drug substance manufacturers' in ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) terminology.

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