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# Common or distinct INN for biosimilars? Only characteristics of the active substance prior to formulation should be considered

Professor Paul J Declerck, PhD

## To the Editor:

I read with interest the letter of Dr Edward T Maggio which was published in Volume 2/Year 2013/Issue 4 of the *Generics and Biosimilars Initiative Journal* [1] on the naming issue for biosimilars and traceability of immunogenicity. He states that during storage of a biological drug product the active substance may undergo aggregation and oxidation. Dr Maggio also states that these processes are influenced by excipients such as polysorbates. In the context of the currently hot debate on the designation of the International Nonproprietary Name (INN) of biosimilars it is concluded by the author that biosimilars should be given an INN that is distinct from the INN of the reference product. The arguments are based on the fact that the formulation of the biosimilar is different from that of the reference product, subsequently leading to distinct product-related variants over time in both drug products. This may then result in a different safety profile. I would like to point out that any given INN is based on the structural characteristics of the purified active substance prior to formulation. Any subsequent modifications that happen during or after formulation or storage should not be the subject of the INN. I therefore feel that in the discussions on whether or not the active substance of a biosimilar should be given a distinct INN, neither the formulation nor possible changes upon storage should be taken into account.

**Dr Edward T Maggio's reply:**  
Professor Paul Declerck's response would be correct if the linear sequence of a biotherapeutic is the sole determinant of its biological

activity and that changes to the immunogenicity profile of the bioactive protein due to differences in formulation are irrelevant to clinical utility. Neither assumption is correct. For example, glycosylation, a common post-translational modification that has a critical role in antibody effector function is determined by the manufacturer's proprietary manufacturing process which can and almost certainly does differ from process to process. As pointed out by Zheng et al. [2] differing glycoforms may lead to alteration of a biotherapeutic's intrinsic properties and stability resulting in differing therapeutic efficacies. INN numbers will be used by third party payers and others assembling formularies that designate approved and reimbursable drugs under the false presumption that all drugs having the same INN designation are clinically equivalent. Since differences in immunogenicity resulting from differences in formulation and changes during storage, e.g. neoantigen formation due to polysorbate-driven oxidative damage, may create significant and serious differences in clinical outcomes, for example, due to differences in neutralizing antibody development or anaphylactic responses. Such drugs would be not at all bioequivalent clinically and they should remain distinguishable so that physicians and patients can make informed judgements as to which drug they wish to employ. Perhaps an INN number consisting of two parts, a common stem relating to the structural similarity of the biotherapeutic followed by suffix specific to each manufacturer's product, would be the best means to simultaneously designate the similarity of anticipated clinical utility among related biosimilars, as well as provide a traceable marker of each individual product

to allow direct comparisons in post-market surveillance as required by the US Food and Drug Administration and the European Medicines Agency.

## Professor Paul Declerck's reply:

Dr Edward T Maggio's response and argument ignores the scientific fact that the term post-translational modifications concerns the 'active substance' for which manufacturing conditions (up to isolation of the purified active substance) indeed can affect glycosylation and so on. Per definition only the properties up to this step, i.e. purified active substance, can be taken into account for the INN (INN refers exclusively to the name of the active substance prior to formulation), e.g. differences in glycosylation do not occur after formulation! Consequently, even though changes induced by formulation and storage at the level of drug substance do indeed occur and may have an impact on immunogenicity, these can never be taken into account for INN issues. For example, this would imply that the INN might change during storage and that we need different INNs for the same active substance produced by the same manufacturer but presented as two different formulations, e.g. different administration routes. It needs to be stressed that this does not mean that differences in formulation are irrelevant to safety or clinical issues. That is why biologicals/biosimilars produced by different manufacturers must be distinguished by different brand names.

**Competing interests:** The author has no conflicts of interest that are directly relevant to the content of this manuscript.

**Provenance and peer review:** Not commissioned; internally peer reviewed.

## References

1. Maggio ET. Critical immunogenicity differences will be obscured by a common INN for biosimilars. *Generics and Biosimilars Initiative Journal (GaBI Journal)*. 2013;2(4):166. doi:10.5639/gabij.2013.0204.046
2. Zheng K. The impact of glycosylation on monoclonal antibody conformation and stability. *MABs*. 2011 Nov-Dec;3(6):568-76. DOI: 10.5639/gabij.2014.0301.003

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Submitted: 24 January 2014; Revised: 29 January 2014; Accepted: 30 January 2014; Published online first: 12 February 2014