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# Critical immunogenicity differences will be obscured by a common INN for biosimilars

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Information about variable immunogenicity arising from formulation differences between competing biosimilars is critical for informed judgments by prescribing physicians. Use of a common INN for biosimilars will obfuscate such differences to the detriment of patients.

**Keywords:** Immunogenicity, INN, neoantigen, neutralizing antibodies, oxidative damage, polysorbate, protein aggregation

Immunogenicity of biotherapeutics is one of the most serious safety concerns of US Food and Drug Administration and European Medicines Agency for obvious reasons. Unwanted immunogenicity can alter or neutralize biological activity of a biotherapeutic in the best case, and in the worst and most well known case, namely erythropoietin, has resulted in patient mortality. Biosimilars and innovator biotherapeutics can differ significantly in the degree of unwanted immunogenicity. Two principal sources of immunogenicity are protein aggregation [1] and oxidative damage caused by the inclusion of polysorbate excipients in many if not most biotherapeutics – innovator products as well as biosimilars alike. Aggregation induced immunogenicity is a function of the extent and nature of the aggregates formed which in turn is determined in large part by differences in the chemical composition of the biotherapeutic. Oxidative damage is caused by reactive peroxides, epoxy acids, and aldehydes, which spontaneously arise and which are found in all lots of polysorbate 80 (Tween 80) and polysorbate 20 (Tween 20) and which vary over a 26-fold concentration range. These reactive species progressively generate neoantigens *in situ* during product storage by reaction with aminoacyl sidechains – a principal source of unwanted immunogenicity. Since the factors that determine unwanted immunogenicity, namely amino acid sequence/glycosylation and the composition of the reactive components arising from excipients such as polysorbates in the aqueous vehicle, are likely to vary between innovator and biosimilar, as well as between one biosimilar to the next, failure to differentiate each product by enforcing a common INN (International Nonproprietary Name) deprives physicians of essential information in differentiating and understanding differences in the product safety and efficacy profile of each therapeutic alternative. Lastly, differences in the immunogenicity profile of biotherapeutics often only become apparent once the product has been administered over an extended time to a large group of patients. Simply because biotherapeutics, no matter how similar, are not all equal, one or more of the biosimilars may eventually be identified as 'biosuperior' with respect to reduced or eliminated immunogenicity compared to the other corresponding products (biosimilars and innovator alike). Use of a common INN [2] will obfuscate these important differences to the prescribing physician to the detriment of patients whose health, and perhaps life, depend upon the physicians informed judgment.

**Disclosure of financial and competing interests:** Dr Edward T Maggio is the CEO of Aegis Therapeutics LLC. Aegis does not manufacture or sell any biotherapeutics. Neither Dr Maggio, Aegis Therapeutics, or any Aegis officer own any shares of companies that do so.

However, Aegis out-licence formulation technologies for small molecules and biotherapeutics, this may be indirectly related to the issue focused on in the Letters to the Editor (INN naming of biosimilars).

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## References

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