In principle, the biosimilar concept applies to all biological drug submissions. In practice, similarity is demonstrable only on products that contain well-characterized drug substances, typically recombinant proteins. For this reason, drug substances that are more difficult to characterize, such as those sourced from organs, tissues, or fluids are less prone to, not to say excluded from, biosimilar applications. The same perception prevails for vaccines that are usually excluded from the scope of biosimilar guidelines. Whereas complex vaccines such as those including conjugate polysaccharides would indeed be difficult to characterize, recombinant protein vaccines could be easier to copy. By the way, the Japanese guideline differs from other guidelines since well-characterized recombinant vaccines can possibly be developed as follow-on biologics (Yamaguchi and Arato, 2011). As for the live attenuated vaccine, although this view is not universally shared, the authors have no objection in principle to their possible development under the biosimilar approach. Such applications would obviously require clinical studies, but these might be significantly lighter than the full clinical development of the vaccines and could possibly be based on surrogate markers, making this an attractive approach.

More than a decade may elapse between the application for an originator and for its copy. In the meantime, the technology will have changed with the emergence of possible new production processes and more powerful analytical methods. This gives rise to biosimilar products that are more effectively controlled, display a higher purity and show a better lot-to-lot consistency. In this context, paradoxically, a lesser similarity of biosimilars to their reference would merely be the result of a better quality, in stark contrast to their negative image of wrongly alleged second-grade products (Schneider, 2013).

The improvement of physicochemical and biological analytical methods is also pushing forward the biosimilar paradigm. State-of-the-art, more powerful methods allow detection of subtle differences in the quality profiles of the biosimilar and the reference, and the greater the resolution of the analytical methods used, the more heterogeneity will be apparent (Kozlowski and Swann, 2006). The former question, "*are the methods sensitive enough?*" is now changing to "*what do differences mean?*" (quoted from Schneider, 2011). The most straightforward way to answer this latter question would be to conduct additional animal and/or human testing, while the biosimilar pathway is aimed primarily at reducing the burden of the nonclinical and clinical development. In addition, the clinical measurements have their own relatively large variability. As a consequence, it is not unlikely that the power of standard scale clinical trials will not be sufficient for revealing the clinical impact (if any) of slight quality differences. Finally, assuming that there is a minor, hardly detectable but established impact of quality differences on the clinical performance of a biosimilar, do these subtle differences really matter? Where knowledge acquisition through clinical studies is neither technically, ethically, nor economically feasible, instead of relying on the premarketing clinical development, experience could be gleaned from the postmarketing pharmacovigilance which thus appears of particular significance for biosimilars.

Finally, and it is not the least odd feature of biosimilars, demonstration of biosimilarity against the reference product is a "one-shot" exercise to be achieved