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Optimizing clinical trials as part of the totality of data to support the marketing approval of biosimilars

The prevailing view is that the structure of biosimilars cannot be established or even manufactured to be identical to the original product. This residual uncertainty needs to be addressed by bridging clinical data, which generally includes a PK (pharmacokinetic) and a therapeutic equivalence trial. However, very limited consideration has been given to what this residual uncertainty is and the extent to which such trials could be suitable or are necessary to address this perceived uncertainty. While it is true that structural differences are possible between the reference product and the biosimilar and that such differences may impact PK, potency, immunogenicity and safety, the generally proscribed clinical trial program may not always be the appropriate approach to discerning the impact of such differences. In fact such structural changes have also been observed to occur due to process changes introduced in the manufacture of the reference product with no requirement for supporting clinical data. Looking at this objectively, PK can usually be effectively addressed in clinical trials often in healthy subjects; in most cases these are relatively straight forward trials to perform and provide clear evidence for PK equivalence. Potency on the other hand is generally required to be studied in therapeutic trials but the value of such trials is debatable. Often the therapeutic dose may lie on the flat part of the dose response curve so that even if a difference in potency existed it would not be detected whereas *in vitro* methods are far more sensitive to detect differences. There are also considerable challenges in designing and executing therapeutic equivalence trials whereas in fact it is immunogenicity and safety where residual uncertainty remains, and which needs to be addressed in clinical trials.

Recent Publications

1. Kozlowski S et al. (2011) Developing the nation's biosimilars program. N. Engl. J. Med. 365:385-388.
2. Weise M et al. (2012) Biosimilars: what clinicians should know. Blood 120:5111-5117
3. Schellekens H and Moors E (2010) Clinical comparability and European biosimilar regulations. Nature Biotechnology. 28:28-31.
4. Weise M et al. (2014) Biosimilars: the science of extrapolation. Blood. 124(22):3191-3196.
5. Bennet C L (2014) Regulatory and clinical considerations for biosimilar oncology drugs. Lancet Oncology 15(13):e594-e605.

Biography

Cecil Nick holds BSc (Hons) in Biochemistry from the University of Cape Town, South Africa. He has been the Regulatory Affairs Professional for over 30 years. He has expertise in monoclonal and biosimilars, having worked on over 20 such programs, engaged in over 50 interactions and meetings with regulatory agencies in the EU, US, Canada, Australia, Mexico, Brazil and supported 6 submissions in the EU and US. He has also participated extensively in industry and international meetings on the subject. Prior to joining Parexel, he served as Regulatory Manager at Novo Nordisk Ltd, Fellow of TOPRA and has been a Guest Lecturer at Cardiff University for MSc in Clinical Research and Greenwich University for MSc in Pharmaceutical Sciences courses and Biotech Module Leader for the TOPRA MSc course. He was on the Editorial Panel of *Scrip Clinical Research* and has authored many articles on Regulatory and Clinical Development Issues.

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