EU approval of a biosimilar product is conditional on a heightened level of postauthorization risk management provisions: most notably, warnings and precautions in prescribing information and product labeling, focused pharmacovigilance, and, in some cases, commitments to perform postapproval interventional clinical studies and/or establish patient registries to monitor particular safety concerns.

While postauthorization studies are unlikely to provide the same quality of data as randomized controlled preauthorization studies, they do have potential to provide evidence of sustained benefit-risk under real-world conditions, that is, where patients to be treated are not preselected to meet stringent inclusion and exclusion criteria. In the case of immunogenicity, observational cohort studies have contributed highly instructive information on the relationship between sustained efficacy, steady-state drug concentration, and ADA formation for adalimumab (Bartelds et al., 2011).

Thus, a prospectively designed, noncomparative, observational cohort study could provide postauthorization evidence of reduced drug concentration and loss of efficacy causally related to formation of ADAs—which may then be compared with historical information for the reference product. This would require a "low-intervention" type study, in the sense that periodic blood samples would be collected for measurement of drug concentration and ADA, and patients would also be monitored for sustainability of efficacy and for adverse events of particular relevance, for example, injection-site and hypersensitivity reactions.

Information on the relative incidence of serious adverse events associated with treatment by different versions of the same molecule, that is, the reference product and different approved biosimilars, could be accumulated from patient registries. While patient registries can be useful to monitor the incidence of targeted serious adverse events and, in some cases, sustained benefit (via "drug survival" rates), immunogenicity is rarely measured. Thus, the prospectively designed, postauthorization, observational cohort study would seem to offer the best opportunity for monitoring the impact of the long-term immunogenicity of approved biosimilar products—albeit in a noncontrolled (noncomparative) sense.

All approved products are subject to periodic reevaluation of benefit-risk by regulatory agencies. This would include a review of spontaneous adverse event reports and published literature to identify immune-mediated adverse events.

One potential gap is incomplete transparency of data accumulated during the postauthorization phase for different biosimilar products, which could be addressed by periodic updating of the detailed information provided in the EPARs issued at the time of the initial approval, to include outcomes of provisions in the Risk Management Plan. In addition, lack of harmonization across EU member states for regulatory requirements for conduct of postauthorization, observational cohort studies involving relatively low interventional impact could discourage such studies. The implementation of a "low-intervention" designation for prospectively designed observational studies of approved products, involving periodic blood sampling to measure steady-state drug concentration relative to ADA formation, and monitoring of sustained efficacy and targeted adverse events, may create a possibility for such studies to be approved only by the concerned Ethics Committees—without a need for national regulatory agency approval.