or infliximab, thereby causing a nonelective (either for the physician or patient) switch. Such switches have not yet identified an increased immunogenicity-related risk for the EU-approved biosimilar products, and there was not a single signal in the EudraVigilance serious adverse event database as of May 2015 (FIMEA, 2015).

Switching studies are not part of the current EU regulatory requirements for approval of biosimilar products, as there is an implicit understanding that a candidate that meets the rigorous approval standards for biosimilarity *can* be regarded as a therapeutic alternative to the reference product (Weise et al., 2012). The regulator's decision to approve the biosimilar version serves as an adequate basis to allow physicians to make the choice on whether to switch a patient from a reference to a biosimilar version, or vice versa. This consideration applies to the efficacy, safety, and immunogenicity dimensions of the overall clinical benefit-risk assessment. To date, this position has been publicly affirmed by the authorities of four EU member states, namely, Finland, Germany, Ireland, and The Netherlands (Ekman, 2016).

Biosimilar development programs for some chronic administration products have included controlled transition between treatments, with the intent of reinforcing prescriber confidence in the biosimilar version as well as to satisfy scientific advice received from the FDA. However, the discriminatory sensitivity of such study designs is rather questionable, not least because of the potentially confounding influences associated with the persistence of therapeutic effects and immune responses to the previous treatment (Ebbers and Chamberlain, 2014). This severely limits the feasibility of designing clinical studies to demonstrate interchangeability as required by US legal statute, if measures of clinically relevant immunogenicity of the different product versions were to be included as part of the evidence. Without very long (6–18 months, depending on the product) drug washout periods—which may be considered to be unethical—the clinically relevant parameters would be confounded by effects (pharmacodynamics and immune response) associated with earlier treatment. Low feasibility could explain why there are so few examples of well-controlled switching studies for different versions of therapeutic proteins.

One soundly controlled study that evaluated switching between two *distinct* human Factor VIII products (with different primary amino acid sequences, i.e., not biosimilar) showed that switching had no impact—even in the case of intentionally modified versions of a molecule that has identified immunogenicity-related risks (Hay et al., 2015).

The directly comparative switching experience gained for infliximab, in which subjects treated for 52 weeks with one version of infliximab were either switched to a different version or maintained on the same version (Park et al., 2013; Yoo et al., 2013) for a further 12 months, revealed a remarkably similar level of ADA incidence in rheumatoid arthritis patients, and only a marginally higher numerical difference in ankylosing patients (Figure 12.4).

The comparative design of the NOR-SWITCH study (NCT02148640) incorporates measures of relative anti-infliximab antibody formation in some 500 patients stabilized on the reference product, who are then randomized 1-to-1 for continuing treatment on either Remicade ($n = 250$) or Remsima ($n = 250$) for a 52-week period. Results from this study indicate a comparable incidence of treatment-emergent ADA for patients switched to Remsima compared to those remaining on Remicade (Jørgensen et al., 2016).