subcutaneous administration of epoetin alfa in renal anemia, and a separate noncomparative safety study was performed using subcutaneous administration in oncology patients (Chamberlain, 2014).

Regulatory agencies may be more reluctant to extrapolate conclusions about relative immunogenicity from the oncology to autoimmune disease setting for rituximab, although long-term safety studies have not revealed a clear negative impact associated with ADA formation during chronic administration of rituximab to treat rheumatoid arthritis (van Vollenhoven et al., 2010).

Since healthy volunteers will be fully immune competent, measurement of AUC0-infinity following a single administration of adalimumab to healthy volunteers could provide the most sensitive endpoint for detecting a difference in clinically impactful ADA formation.

Concomitant use of immunosuppressive medication is not the only consideration for assessing the suitability of the clinical population(s) to be evaluated: in the case of infliximab (EPAR for Remsima), the ankylosing spondylitis population (no concomitant MTX) had a lower detected incidence of ADA compared to the rheumatoid arthritis population (treated with concomitant MTX), possibly due to higher residual drug interference in the ADA assay associated with the higher dose level used in the ankylosing spondylitis indication. Thus, detectability of the ADA response as well as the relationship of the ADA response to adverse outcomes will need to be considered in choosing the most suitable conditions under which to evaluate immunogenicity.

Chronic administration therapeutic efficacy studies may have relatively low discriminatory power for detecting a potential influence of lower/higher relative immunogenicity on efficacy if the drug is dosed at a supramaximal level in terms of the dose-efficacy response curve, and/or the clinical efficacy endpoints are associated with relatively high intersubject variability in pharmacological responsiveness. In addition, therapeutic equivalence studies are not powered to enable a statistically rigorous comparison of safety signals—which may be more accurately estimated in the longer-term postauthorization setting (e.g., via interventional observational cohort studies).

In summary, the experience gained to date for the EU-approved biosimilar products has strongly substantiated the practice of extrapolating immunogenicity findings across all therapeutic indications authorized for the reference product; or, in the case of epoetin alfa, of justifying the requirement for additional evidence prior to authorization for use in higher risk settings.

12.24 SWITCHING

An elective decision by the supervising physician to switch patients between medications that can be expected to achieve the same therapeutic effect is part of routine medical practice. An extensive review of the experience gained from switching patients between different versions of the same biological product, or even between different biological products licensed for the same therapeutic indication (Ebbers et al., 2012), did not reveal evidence for an increase in immunogenicity-related risks that were associated with switching of medications. In the EU, switching experience has been accumulated as a result of local tendering processes leading to a decision to procure a biosimilar version of somatropin, filgrastim, epoetin alfa, insulin glargine,