EU regulatory guidance indicates that in certain cases, it may be possible to justify omission of directly comparative evaluation of clinical immunogenicity (EMA, 2014c); this might be the case for less complex recombinant proteins (e.g., teriparatide) that can be adequately characterized by analytical methods and have not been associated with clinically impactful immunogenicity.

If a sponsor is seeking to extrapolate immunogenicity findings for one condition of use to other conditions/therapeutic indications, the sponsor should consider using a study population and treatment regimen that are sensitive enough to predict a difference in the *adverse effects* associated with immune responses to the proposed product and the reference product across the different conditions of use. Usually, this will be the population and regimen for the reference product for which development of immune responses with adverse outcomes is most likely to occur (FDA, 2015). In the case of insulin, treatment-naïve subjects are likely to provide a more sensitive test of relative immunogenicity (and its clinical impact) than previously treated patients, explaining why both populations were included in the preapproval studies for Abasaglar (EPAR for Abasaglar). Thus, a different study population could be used for comparing immunogenicity from that used to demonstrate comparable efficacy.

For chronically administered agents, EU guidance recommends monitoring antibody formation during a comparative treatment period of 6–12 months, depending on the product. FDA guidance recommends that the extent of monitoring be based on the identified risks for the particular product. In the case of chronically administered agents, however, the posttreatment follow-up monitoring period for ADA positive subjects should be one year, unless a shorter duration can be justified.

In the EU, a biosimilar candidate could have lower immunogenicity than the reference product, provided that this did not result in a significant and clinically relevant increase in efficacy. FDA guidance (FDA, 2015) cautions that differences in immune responses between a proposed product and the reference product in the absence of observed clinical sequelae may be of concern and may warrant further evaluation (e.g., extended period of follow-up evaluation).

As emphasized already, interpretation of bioanalytical results for ADA formation should always be correlated with clinical measures because (1) bioanalytical assays are more or less confounded; and (2) there is no clearly established relationship between ADA response dynamics and clinical impact (due to a lack of bioanalytical assay standardization and objective assay controls) for any product.

12.18 WHAT TO MEASURE

The clinical immunogenicity evaluation should seek to measure the following comparative indices of the humoral response to the biosimilar and reference products:

- Confirmed ADA positive versus ADA negative incidence in pre- versus posttreatment samples, distinguishing between transient versus persistent antibodies if relevant;
- ADA titer or other index of magnitude (%B/T for insulin, which represents proportion of total antigen binding in radioimmunoassay, a measure of anti-drug antibody formation);