- Neutralizing capacity of confirmed ADA;
- Relative time-course of ADA (neutralizing and nonneutralizing) detection;
- Cross-reactive capacity of ADA (e.g., insulin glargine vs. endogenous insulin);
- ADA reactive with process-related impurities (e.g., host cell-derived proteins, if relevant).

Although monitoring of cell-mediated immune responses has not been a feature of the immunogenicity evaluation for the biosimilar products approved to date, there might be value in comparing the *in vitro* responses of innate and adaptive immune effector cells (e.g., to exclude a potential influence of differences in drug product formulation on the stability of a therapeutic protein). However, this is not a current regulatory requirement.

12.19 PRESENTATION OF DATA

Questions from regulatory agencies about the suitability of ADA assay methodology have been very common for the biosimilar applications reviewed to date. EU regulatory guidance has been updated (EMA, 2015) to encourage sponsors to submit an integrated summary of immunogenicity as part of the application for marketing authorization. The author's format for a biosimilar candidate includes the following subheadings:

1. Identified risks and uncertainty for reference product
2. Control of product quality-related risks
3. Suitability of bioanalytical methodology
4. Results of comparative clinical evaluation
5. Conclusions about relative immunogenicity
6. Recommendations for ongoing risk management.

Under subheading (3), the rationale for selecting particular methods and assay controls can be presented in relation to a critical discussion of the validated method performance characteristics. The author has found it helpful to include this integrated summary within CTD Section 5.3.5.3, since this provides more flexibility to include more tabular and graphical data than is possible in Module 2.7.2.4.

12.20 EXTENT OF CLINICAL EVALUATION

Data on ADA incidence and titer from both comparative PK (Phase 1) and therapeutic equivalence (Phase 3) studies have contributed to the assessment of immunogenicity for most of the biosimilar products approved in the EU (Chamberlain, 2014). Exceptions were filgrastim, for which therapeutic equivalence was established in comparative PK/PD studies, supported by a safety study (EPAR for Zarzio), and biosimilar insulin glargine (Abasaglar), where the EPAR reports immunogenicity data from the two, 52-week duration, Phase 3 studies, but not from the Phase 1 PK/PD studies.