

TABLE 12.3 (Continued)
Product Quality-Related Factors for Differential Immunogenicity of Biosimilars

| Risk Factor | Risk Evaluation | Risk Mitigation |
|---|--|--|
| Altered pattern of positional isomerization of polyethylene glycol-conjugated protein | Comparative peptide mapping to define quantitative profile of positional isomers | Analytical characterization demonstrates highly similar structural profile, including distribution of positional isomers |
| | Process variables influencing site-specific conjugation | Adequate manufacturing process control to ensure consistency of quality profile |
| | Comparative clinical studies to measure ADA response using commercial drug product formulation–primary container combination | No increase in clinically impactful ADA to any component of the drug product |
| Differences in qualitative or quantitative composition of host cell-derived, or other process-derived, impurities | ADA monitoring includes suitable method to detect polyethylene glycol-reactive antibodies in pre- and posttreatment samples | |
| | Two-dimensional gel electrophoresis (charge + size separation) with silver staining and Western blotting detection to identify host cell-derived protein profile | Analytical assays validated for suitable specificity and sensitivity to detect process-related impurities |
| | Application of process-specific host cell protein assay; assays for other impurities as relevant | Downstream process design enables effective removal of process-related impurities |
| | Demonstration of effective clearance of process-related impurities by downstream process | Suitable drug substance/drug product release limits for process-related impurities |
| | Comparative clinical studies to measure ADA response using commercial drug product formulation–primary container combination | No increase in clinically impactful ADA to any component of the drug product |
| | Cross-reactivity testing of ADA signals detected in pretreatment samples from clinical studies | |

ADA, antidrug antibody; Neu5Gc, *N*-glycolyl neuraminic acid; Gal, galactose.

12.7 IMPLICATIONS OF PRODUCT QUALITY VARIABLES FOR REGULATORY ASSESSMENT

Any detectable differences in variables that represent identified risk factors in Table 12.3 should be justified by demonstrating an absence of a difference in *clinically impactful* immunogenicity of the biosimilar candidate relative to the reference product.