12.6 CONTROL OF CRITICAL PRODUCT QUALITY ATTRIBUTES FOR IMMUNOGENICITY-RELATED RISKS

Immunogenicity-related risks for biosimilar candidates need to be effectively controlled at the manufacturing and product quality testing levels. With the advance in analytical technologies, the risk of incremental immunogenicity can be evaluated and, to a large extent, avoided by analytical characterization, batch release testing, and stability testing. Clinical evaluation with appropriate bioanalytical testing then provides confirmatory evidence of comparative immunogenicity.

Thus, although the starting materials, cell substrate, manufacturing process, product formulation, and primary container might all be different from those used to produce the reference product, the impact of these variables on identified risk factors for undesirable immunogenicity of the molecule can be detected if an appropriate combination of methods are applied for analytical characterization and stability testing.

The evaluation and mitigation measures for potential immunogenicity-related risk factors associated with the product quality of biosimilar candidates are summarized in Table 12.3.

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

Risk Factor	Risk Evaluation	Risk Mitigation
Instability of the active substance	Formulation development studies	Adequate justification for any differences in product formulation
	Compatibility of drug product with primary container	Choice of suitable primary container
	Definition of stability-indicating quality attributes	Overlapping analytical profiles for relevant quality attributes of biosimilar versus reference product
	Comparative stability of commercial drug product formulation–primary container combination under forced degradation conditions linked to analytical characterization of relevant quality attributes	No increase in clinically impactful ADA for biosimilar drug product to be marketed
	Extended analytical characterization to include methods sensitive to detect differences in primary and higher-order structure and thermal stability	Clear instructions on handling and storage conditions, allied to adequate supervision of supply chain
	Comparative clinical studies to measure ADA response using commercial drug product formulation–primary container combination	

(*Continued*)