proteins, and no increase in clinically impactful immunogenicity that could be ascribable to an unacceptably high level of residual host cell-derived protein.

The potential for formulation differences to influence drug product stability in a manner that might not be detected by analytical methods applied for routine drug product batch release testing increases the importance of conducting (as early as possible in the biosimilar product development program) comparative stability studies using forced degradation conditions. In the author's experience, it is possible that, even when the same qualitative and quantitative composition of excipients is used to formulate the biosimilar product compared to the reference product, there may be a measurable difference in pH range—necessitating a slightly different specified pH range for the biosimilar drug product version. Acceptability of such a difference should also be justified by comparative stability studies and exclusion of the potential for increased clinically impactful immunogenicity.

12.8 EXAMPLES OF POTENTIAL PRODUCT QUALITY ISSUES IDENTIFIED IN THE PREAUTHORIZATION PHASE

Some examples of potential immunogenicity-related concerns arising from analytical differences detected in the preauthorization phase for different biosimilar candidates are summarized in Table 12.4.

In all cases, the regulatory process was effective in identifying and mitigating a potential increase in the immunogenicity-related risk. For Binocrit, this involved additional clinical evidence prior to approval for subcutaneous use in renal anemia; the purification process for the approved version of Omnitrop was modified to

TABLE 12.4
Impact of Quality-Related Risk Factors Identified in Preauthorization Phase for Candidate Biosimilars

Detected Quality Difference	Impact
HMW variants associated tungsten residue (Binocrit) Ref: Seidl et al. (2012)	Possible association with induction of neutralizing ADA in two subjects; one confirmed case of amPRCA (CKD SC route only); change to low-tungsten prefilled syringe
E. coli HCP impurity (early version of somatropin) Ref: EPAR for Omnitrop	Treatment-emergent antibodies to HCP and reported enhancement of ADA reactive with somatropin; additional purification step to remove HCP impurity
Higher level of Neu5Gc Ref: EPAR for Ovaleap	No impact of preexisting Neu5Gc-reactive antibodies on PK
Different product-related impurity profile Ref: EPAR for Alpheon	No apparent difference in immunogenicity; not authorized because analytical comparability not adequately demonstrated

HMW, high molecular weight; amPRCA, antibody-mediated pure red cell aplasia; CKD, chronic kidney disease; SC, subcutaneous; HCP, host cell protein; ADA, antidrug antibody; Neu5Gc, *N*-glycolyl neuraminic acid; EPAR, European Public Assessment Report.