Table 27: Immunogenicity: Impact on Therapeutic Proteins

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**SCOPE:**
Companies often use a risk-based approach to develop a severity assessment to identify critical quality attributes (CQAs) by evaluating potential impact of the quality attributes on the safety and efficacy of the product. One of the categories assessed is immunogenicity.

Immunogenicity is the ability of a substance to induce an immune response. An unintended immune response can have severe consequences especially in an already sick or vulnerable population. Antibodies to the biotherapeutic can be neutralizing or non-neutralizing, and potentially change the efficacy of the product, or effect the safety of the drug. A safety profile of a therapeutic protein is established throughout the development process. Changes in raw materials and the manufacturing process must be critically evaluated to understand the potential impact on this profile. This evaluation includes an assessment of the impact on immunogenicity.

Although guidance exists for providing immunogenicity assessments for therapeutic protein products approaches used by companies vary. The focus of this discussion is to understand some of the approaches used and to share best practices.

**QUESTIONS FOR DISCUSSION:**
1. What quality attributes does your company assess when evaluating potential impact on immunogenicity?

2. What changes in raw materials and the manufacturing process have led to impacts related to immunogenicity?

3. Do you have experience with a change that initially was assessed as having a negative impact on immunogenicity, but upon further evaluation was determined not to have an impact on the overall safety and efficacy of the product?

4. How do you assess impact on immunogenicity for a product which itself is expected to produce an immune response resulting in most patients developing anti-drug antibodies? Relative immunogenicity?

5. What types of *in silico*, *in vitro*, and *in vivo* model systems do you use as part of your immunogenicity assessment?
DISCUSSION NOTES:

- **What are implications of immunogenicity to therapeutic proteins?**
  - Differs by patient population, type of protein, route of administration
    - For native protein it is severe, as compromises activity of endogenous protein as well: Discussed EPO and PRCA as one example

- **Patient population can be very important, and not always covered during early clinical studies**
  - Factors for treating hemophilia saw neutralizing antibodies when product used in Japan, different HLA in this patient population
  - Important to include genetic diversity whenever possible in all assays including cell based.

- **Discussed difference between Product quality attributes, which are monitored as part of process consistency, and critical quality attributes, which are part of safety and efficacy. (CQAs). Immunogenicity is a CQA**

- **How are the predictive assays used?**
  - Tiered strategy, starting with in silicon and then to invitro, most often during development, as risk mitigation/risk assessment
    - Choose best candidates,
    - Understand CQAs,
    - Computational methods used but of limited utility
    - Cell based assays,
      - APC and proteins. Looking at peptide seq bound
      - Cytokine activation of different cell lines or primary cells (PBMC)
      - Should include patient population route of administration, etc.
  - For reviewers, seeing the data is a good piece, but is not clinical results
  - Lot specific pharmacovigilance would be very valuable, and understanding role of biology

- **When assessing immunogenicity, a holistic approach is needed as other factors in addition to the API can contribute including, but are not limited to:**
  - inactive ingredients (excipients),
  - HCP
  - contact surfaces (vial, device, and administration sets)

- **Raw material components and consumables, such as complex media formulations and cell culture bags, respectively, should be assessed for immunogenetic risk(s) and clearance capabilities**
  - Examples include gluten, casein and extractable/leachables.