Table 9: Current Analytical Challenges in the Immunogenicity Assessment of Therapeutic Proteins

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DISCUSSION:

1. Discussions around risk assessment of immunogenicity
   a. Risk assessment per ICH Q9 is undertaken to identify product and patient and clinical trial related risks
   b. Initial assays to look at when to begin looking at immunogenicity based on risk assessments include:
      i. Sequence analysis for B T cell epitopes
      ii. HA typing
   c. Companies are receiving increased number of questions regarding their approach to assessing immunogenicity
   d. Questions are becoming more sophisticated:
      i. Historical questions included “Are the ADAs neutralizing?”
      ii. Contemporary questions include, “What part of the drug molecule does it bind? What is size of immune complex? (pre-clinical finding)”

2. Discussions on immunogenicity case studies and increasing our understanding of immunogenicity
   a. One company observed an isolated case of immunogenicity with Factor VII in pre-clinical studies. Concerns about cross reactivity resulted in termination of the program. Other companies have also terminated Factor VII programs.
   b. FDA has not seen a program terminated because of a single case of immunogenicity. Gaining an understanding of the product and knowledge of literature is critical.
   c. An increased knowledge of the genetic background of patients may improve our knowledge of immunogenicity
   d. Experience with immunogenicity is limited amongst sponsors as only a few patients may have an immune response. Can companies collaborate to gain better understanding
   e. The infamous case of immunogenic Epo is likely due to product abuse (effect was localized, drug was self-administered by the patient, reports of milky epo).
3. Discussion around when should a sponsor bring an assay to FDA for review
   a. A validated assay is required to assess immunogenicity in Phase 3. However, one case where potential immunogenicity was seen in an in vitro assay
   b. Standard approach: collect samples until ADA assays can be run
   c. Feedback usually given right away at Type C meeting

4. Discussions on baseline immunogenicity
   a. Anti PEG antibodies have been observed in 20% of population
   b. FDA is recommending that companies set up a screen for anti-PEG antibodies for appropriate products to establish baseline and enable monitoring
   c. Anti-yeast is also a common ADA
   d. Screening assays typically look for IgGs. IgGs stem from a mature immune response, most ADAs are IgM. IgE is challenging to measure, one typically has to look for anaphalactic response in clinic

5. Discussions on the acceptability of commercial kits for immunogenicity
   a. At most companies, immunogenicity assays are developed in-house (ligand binding). Common questions from reviewers have focused on the controls in the kit
   b. FDA: most assays seen in filings are in house. Must bridge lot to lot.
   c. Challenge of using a commercial kit: information about the kit is often proprietary, which hinders understanding and data interpretation

6. Discussions around preclinical measurement to clinical monitoring
   a. Extrapolating immunogenicity from animal to human is complex. The key question is does immune complex impact MOA? One isolated case in TPO where preclinical results extrapolated to human
   b. Some programs: drug is initially not immunogenic, but appears later (chronic)
   c. Often, companies stop monitoring after only a year
   d. Recommendation: monitor positive patients to ensure that the immune response not getting worse
   e. Post-market monitoring should also be performed to cover late onset
   f. Low dosing in phase 1 is good for pharmacological safety but it is more beneficial from an immunogenicity perspective to obtain data from high doses.
   g. Sub Q delivery appears to result in greater immunogenicity