Table 4: Strategies for Defining Clinically Relevant Specifications

SCOPE:

Numerous quality attributes are analysed during development and characterization of a biological substance and its corresponding biological medicinal product. Quality attributes may be classified as relevant or critical attributes depending on how they relate to the integrity and functionality of the biological substance.

Adequate safety and efficacy profiles of a biological medicinal product are key to development of a biological medicinal product. It is highly relevant to reveal, how quality attributes ensure the safety of a biological medicinal product and how they mediate efficacy. It is the goal to identify the relationship or link of particular quality attributes to safety and efficacy. Once such parameters have been identified, relevant specifications may be set accordingly.

QUESTIONS FOR DISCUSSION:

1. How do you classify “clinically relevant”
2. How do you verify/establish potential links to clinical safety and efficacy?
3. Do you prefer particular tests for clinically relevant parameters?
4. How do you proceed if
    a. no measurable attributes are identified as link to clinical efficacy/safety?
    b. no obvious link to clinical efficacy is identified?

DISCUSSION NOTES:

- “Clinically relevant” is hard to classify and strongly dependent on the type of biological medicinal product. Proteins (e.g. enzymes or antibodies) are tested in cell-based or non-cell-based assays, therefore the link from *ex vivo* assays to the *in vivo* mechanism of action is difficult to determine. The variability in results of *in vivo* and *ex vivo* assays is a problem. A reproducible plasma matrix for tests would be very helpful.
- For product variants with unknown mechanism of action (*in vivo*) it is important to find an *ex vivo* way to understand.
- Enzyme activity is often not tested in a cell-based assay and is therefore not representative
- A clinically relevant specification should tell if the product is doing what it should be and if it is safe. Even if a specification is set wide, it can tell that something went wrong
- The efficacy is sometimes lost in phase 3, probably due to not reflected surrogates assays