Table 5: Phase-relevant Protein Characterization

SCOPE:

The development of a new biological consists of several phases (pre-clinical, clinical etc.). Due to time and resource constraints, it is not possible or even desirable to analyze and characterize all early-stage candidates to the same extent as market products. But what level of characterization is sufficient for a given phase and what simply isn't? At this table we will discuss how to find a balance between excessive front-loading and too-little-too-late for phase-relevant protein characterization.

QUESTIONS FOR DISCUSSION:

1. Does your company have a procedure for phase-relevant protein characterization (PRPC)? If not, why?
2. To what extent is your company characterizing early stage candidates? Are MAM methods applied?
3. Do you find that "one-size-fits-all" in PRPC? Even for non-platform protein products?
4. Do you experience different levels of regulatory expectations in PRPC in different countries / areas around the world?
5. What would you change to your company's approach to PRPC?

DISCUSSION NOTES:

Notes:

- Figuring out what is really important to characterize in early research and development (R&D)
- Quality control wants products to be well characterized in a very early product stage
- Products in phase 1 should be well characterized and completely characterized at the latest at the beginning of phase 2
    - However normally only a few drug substance batches available this early
    - Accordingly, low statistical power
- In R&D a broad range of methods are applied and the most suitable ones are chosen for characterization and CQAs assessment followed by validation for quality control and product release
    - The goal is to find the right methods as early as possible and focus on them to speed up the developmental process
- A platform approach for characterization of products is only possible if very similar molecules are analyzed, such as monoclonal antibodies. However, new molecules or formats come with different CQAs and, therefore, an individual set of methods need to be

established for each molecule. The principle ‘one size fits all’ is not possible if working in a diverse molecular pipeline.

- Also the first steps of characterization depend upon prior knowledge of the molecule or molecule class. E.g., methods for antibody biosimilars focus especially on the comparability of the glycans to the originator whereas for new formats, e.g. bi- and tri-specifics, the biological activity may be of higher importance.
- Frontloading may be conducted to get as much as possible done in an early stage especially with products that have a high probability of success.
- Still, there are certain methods which are applied throughout most of the molecules such as sequencing, degradation as well as aggregation studies
- Also the therapeutic dose of an API is important to determine when the screening of the formulation as well as the characterization of the drug product is done.
    - For low-dose products, e.g. neurotoxins, the main focus in the drug development will be on the formulation as it can have severe influence on the API. Accordingly, it must be taken into consideration early on to determine its effect at the drug substance level. For high-dose product such as antibodies, the primary focus of characterization will be on the API.
    - For antibodies, extensive formulation characterization is normally conducted in a late stage of development. In early formulation development, the antibodies formulations may only screened with SEC or RP. If the product looks very promising a more detailed formulation development with forced degradation studies is conducted and MS based methods are applied for identification of degradation.
- The extent of characterization are product- and dose-dependent.
    - For example, impurities and host cell proteins in low-dose drugs (e.g. pg amounts with neurotoxins) do not need to be controlled at the same level as, e.g., for antibodies with therapeutic doses in the gram range. Here, host cell proteins occurring at ppm concentrations may yet have significant (negative) effects.
- Currently, multi-attribute methods (MAM) are emerging which generate information on multiple CQAs using a single method of analysis, e.g., mass spectrometry.
    - This is normally used in all stages of development
    - MAM also allows also to get more information on the product in early stage, which can be provided to the authorities.
- The merits of various regulatory strategies were discussed:
    - Giving the regulatory authorities as much information as possible up front versus
    - Giving the regulatory authorities only that information considered immediately relevant and providing additional information upon request.
- Experience in the geographic differences between regulatory authority expectations was exchanged:
    - Within a single authority, large differences in expectations were experienced

A general impression was voiced that European and Canadian may allow flexibility if scientifically justified while Asian regulators e.g. Japanese are less so.