Considerations Regarding Assessment of A Modified Monoclonal Antibody (mAb) Product Related to A Prototype mAb Product in Addressing Emerging SARS-COV-2 Variants – A CMC Perspective

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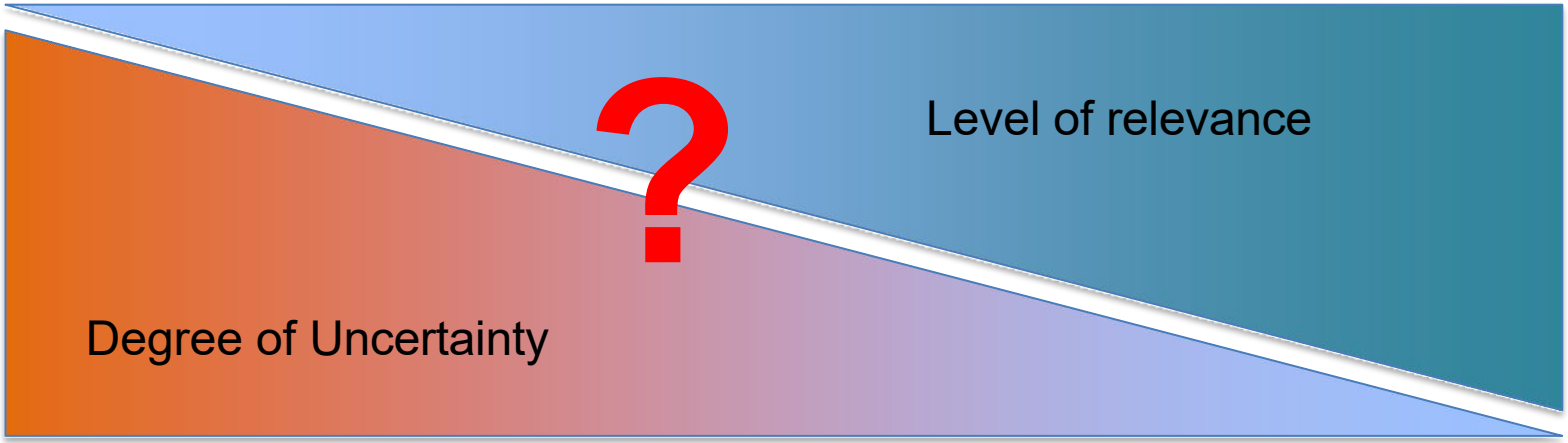
Prototype vs Modified COVID-19 mAbs

- **Prototype mAb**: Existing COVID-19 mAbs product demonstrated to be safe and effective against previous and/or present SARS-COV 2 variants based on a clinical endpoint in randomized, controlled trial(s).

- **Modified mAb**: A new COVID-19 mAb product that is manufactured using the same platform process as the prototype COVID-19 mAb product with the main structural and functional differences limited to variable region sequences and the epitopes to which it binds.

General Principle: Leveraging Existing Knowledge

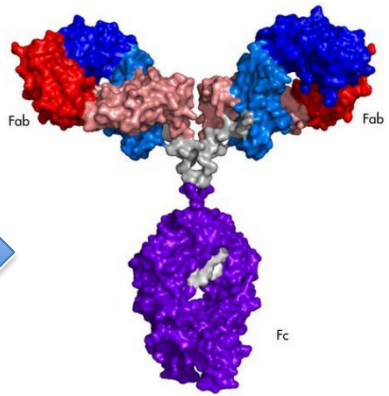


CMC Tools to Potentially Boost the Confidence in the Relevance Level

Product understanding linking critical quality attributes (CQAs) to clinical performance

Platform Technology

- mAb construction and engineering
- mAb expression system
- mAb manufacture



Product characterization

- Structure
- Function

Several CMC Points to Consider
- Potential to Reduce Uncertainty

- Platform expression system: same vectors, same methodology, same engineering/mutation (if present), differences in the construct for variable region sequences designed for the modified mAb

- Platform manufacturing process: Most of the manufacturing process and product controls for the modified COVID-19 mAb should be the “same” (e.g., unit operations, etc.) as that of the prototype COVID-19 mAb. Updated CMC data (e.g., formulation change, differences in scale and process controls, etc.) that are needed to support the manufacture of the modified COVID-19 mAb, will need to be evaluated as a scientific matter.

Several CMC Points to Consider
- Potential to Reduce Uncertainty

- Product characteristics and profile: Thorough product characterization data should be provided to demonstrate the relevance of the prototype mAb product(s) and the modified mAb product. For example,
  - Primary amino acid sequence
  - Secondary, tertiary and higher order structure
  - Post-translational modifications (deamidation, oxidation, glycosylation, etc.)
  - Biologic activities that contribute to MOA (binding affinity and kinetics, neutralization, etc.)
  - Fc effector functions including ADCC, CDC, ADCP, and other assessments

- Any specific Fc-engineering for the purpose of modifying Fc-effector functions or antibody half-life should be the same in the prototype mAb product and the modified mAb product.

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