A number of characteristics of biologics are known to have an impact on the function of the molecule and its safety profile. Some of these properties, such as the formation of aggregates in proteins, are generally recognized as being associated with immunogenicity across product types; others, such as the impact of specific glycoforms of monoclonal antibodies on Fc-related functions, are product class specific. Those characteristics that impact the safety profile of the biosimilar in a negative way are much more likely to *impact the appropriateness of the biosimilar pathway.* It is theoretically possible that some characteristics of a molecule impact the safety profile only under certain conditions, such as subcutaneous versus intravenous administration. However, it is difficult to imagine a situation where extrapolation of data would be possible without direct demonstration of the safety profile to mitigate the risk to patient safety.

More interesting with respect to the determination of extrapolation of data to different indications are the differences that impact certain functions of the molecule but not others. For instance, increased *N*-linked fucosylation of the F_C region of human IgG1 is associated with reduced FcγRIIIa binding and lower antibody dependent cellular cytotoxity (ADCC) activity without appreciable differences in antigen-binding qualities (reviewed in Arnold et al., 2007). The key to demonstrating similarity is that the observed differences in the quality similarity package have no adverse impact on the safety or efficacy of the biosimilar. Thus, a difference between the biosimilar and the RBD limited to a significant difference with respect to afucosylation, FcγRIIIa binding, and ADCC would meet that standard for indications which had been demonstrated to rely on mechanisms of action other than ADCC activity but would fail to meet that standard for indications in which ADCC potentially played a role. The biosimilarity would thus be stratified with respect to the indications, and extrapolation *would not be supported by the quality similarity exercise for indications where FcγRIIIa binding and ADCC played a potential role.*

Setting the bar for quality similarity based on the potential impact on clinical efficacy and safety is a logical approach. However, the application of this approach presumes that the level of understanding of the mechanism of action is sufficiently robust to distinguish the contribution of various mechanisms of action to the clinical efficacy. *In instances where this is not the case, it is the responsibility of the sponsor to support the proposed data extrapolation with sufficient experimental evidence and a detailed scientific rationale.* This evidence and the accompanying rationale must be judged as sufficient to address the residual uncertainty identified during the evaluation of the quality similarity package. Depending on the depth of understanding available in the public domain and the experimental evidence available to the sponsor, it may not be possible to address this residual uncertainty without performing additional clinical studies.

9.3 CLINICAL CONSIDERATIONS

9.3.1 Key Components of the Clinical Studies

The extrapolation of indications requires an evaluation of the totality of the evidence. The quality similarity exercise is an important component for identifying potential gaps in the similarity that may impact the clinical efficacy and safety profile