support the extrapolation of indications. The choice of clinical and nonclinical studies is discussed in detail in the appropriate sections. Regardless of the consequences, the input of the quality similarity assessment to the determination of the extrapolation of indications is the same: *Is there sufficient evidence in the quality similarity package to adequately support the consideration of data extrapolation*? Operationally, this translates into a determination of whether there are specific signals in the data package to indicate a potential safety or efficacy concern with respect to a particular mechanism of action or, more likely, an evaluation of the residual uncertainty regarding the similarity with respect to a particular mechanism of action.

There is a risk in the extrapolation of indications for which there are no primary clinical data. This risk can be mitigated in part by the quality similarity exercise. This mitigation strategy raises high expectations for the quality of the data and the degree of similarity to support biosimilarity. In situations where there is a robust data package that encompasses all of the potential mechanisms of action and all of the quality attributes of the biosimilar product fall within the observed ranges of the reference biological product, the results of the quality similarity exercises clearly support the consideration of the extrapolation of data to other indications. However, the variability of biological products, their labile nature, and the impact of raw materials and the manufacturing process on the CQAs mean that differences are often observed in the quality similarity studies. A number of properties of any biologic may vary without impacting the clinical performance or the safety of the product. Many of these properties are specific to a product class or a specific molecule. In many instances, the relationship between the specific physical chemical characteristics of a molecule and the impact of those characteristics on the clinical efficacy and safety profile are unknown. The relationship between structure and function is explored experimentally both directly and indirectly during the *clinical development of a product*. In the case of innovator products, this clinical experience is often sufficiently robust to predict the impact of certain changes in the characteristics of the product in spite of manufacturing changes.

9.2.3 Dealing with Quality Uncertainty

For biosimilars, which are supported by a comparatively limited clinical program, this product-specific information may not be available. Nonetheless, it is often possible to infer the potential impact of differences in observed characteristics from published product class data to support conclusions regarding the limited potential of the impact of certain differences in some quality characteristics. For instance, there is extensive experience with fully humanized monoclonal antibodies to recognize that a degree of heterogeneity in the C-terminal lysine of human monoclonal antibodies is tolerated without appreciable changes in the efficacy or safety of the molecule. However, in many instances, there may be no reliable information regarding the impact of differences in product-related species. In these cases, the certainty of the quality similarity determination may be impacted, with consequences to potential extrapolation of data. In general, the introduction of a *new molecular species of unknown impact will introduce a greater degree of uncertainty than a variation in the quantity* of a product-related species between the biosimilar and the RBD.