it will then be used to develop the physicochemical window of biosimilarity. With this window of biosimilarity in hand, the biosimilar manufacturer will use it to find the best cell line and experimental growth conditions that will produce a biosimilar that will best match the known physicochemical structural attributes of the RP (see Figure 2.3B).

An important element in assessing an RP's window of consistency and in establishing the window of biosimilarity of a biosimilar is being able to achieve a clear understanding of the challenges and uncertainties via statistical assessments associated with the physicochemical measurements used to generate data to set the boundaries of these windows (Chow, 2015). Without such an assessment, our ability to conduct meaningful biosimilarity evaluations would not be feasible. Consequently, several topics related to the issues that impact the overall uncertainty associated with assessing and establishing these windows will be discussed below under Section 2.5.1 and its subheadings.

2.5.1 Challenges in Assessing the Physicochemical Window of Consistency of an RP in Establishing Biosimilarity

Assessing the physicochemical window of consistency of an RP and using it to develop the physicochemical window of biosimilarity to assess a biosimilar's biosimilarity to its RP would appear to be a fairly straightforward task. Just conduct the same array of appropriate biochemical and biophysical measurements on a number of different lots of the RP and biosimilar and compare the data! However, several important issues that can challenge this process should be considered and evaluated to achieve an accurate and meaningful biosimilar assessment. They include the following:

1. An understanding of each physicochemical method's limit of detection and quantitation used in a biosimilarity assessment and the factors that influence these limits on order to detect and remove any potentially significant bias between the RP and biosimilar owing to a difference(s) in their matrix that includes the sample formulation differences (e.g., buffers, excipients, pH) and residual process impurities differences (e.g., due to the use of different sources of raw materials or different contact surfaces due to the use of different container closures, holding vessels, etc.).
2. An understanding of the potential impact of implementing sample preparation (handling and processing) steps in order to be able to remove bias or interference effects in conducting analytical measurements using a given physicochemical method.
3. An understanding of the impact in only being able to acquire a certain limiting fraction of the total number of (historical) different lots of the RP produced by its innovator and the impact of RP lot age.
4. An understanding of the impact concerning the possibility that a number of the different uniquely labeled RP lots acquired and analyzed by a biosimilar manufacturer were in fact derived from the same bioreactor run rather than from a different bioreactor run.