2.5.1.3.1 RP Lot Age

A source for introducing variability into an RP concerns its level of stability in its container closure during its approved shelf life (when stored within stated storage conditions indicated by the innovator). Although an appropriately formulated biopharmaceutical can prevent or greatly reduce the rate of its degradation so that they never reach the limits for lot rejection (defined by its window of consistency), some level of age-related degradation may occur. Unfortunately, these aging effects do not happen uniformly in all biopharmaceutical container units (e.g., vials, prefilled syringe, etc.). As a result, over time an RP lot's uniformity will diverge from its initial low degradation state when the biopharmaceutical lot was initially released, reaching higher degradation state values, but still within specification values or limits, by the time they reach expiry (typically 2 years later). Consequently, it is important that the biosimilar manufacturer sample RP lots that encompass as wide a range of an RP's shelf life (or lot age) as possible to help assess the RP's full range of variability in terms of its CQAs.

2.5.1.4 Impact of Different RP Lots Derived from the Same Bioreactor Run versus Different Bioreactor Runs

A challenging factor that may lead a biosimilar manufacturer to generate a different window of consistency, relative to that generated by the innovator, has to do with the overestimation of the actual number of uniquely different lots of RP that a biosimilar manufacturer thinks it used to characterize the RP. This arises, as illustrated in Figure 2.7A, when the number of uniquely different-labeled commercial RP lots a biosimilar manufacturer secures are actually derived from the same innovator bioreactor run (see scenario #1 in Figure 2.7A) versus the situation where each commercial RP lot is associated with a unique bioreactor run (see scenario #2 in Figure 2.7A). Since the most significant source for introducing variations into the physicochemical attributes of a biopharmaceutical (especially in terms of PTMs) arises during its biological production (Moroco and Engen, 2015), all lots generated via scenario #1 (Figure 2.7A) will show very similar values for their physicochemical attributes relative to the situation illustrated in scenario #2 (Figure 2.7A), where all lots will show a much greater variability in the value of their physicochemical attributes. This occurs due to the complex and sensitive linkage of cell growth to its physical and chemical environment, which makes the task of replicating the physical and chemical environment inside a bioreactor on a run-to-run basis very difficult. The end result is that the biological production phase of producing a biopharmaceutical is the key source for introducing variability into the biopharmaceutical product relative to the other steps associated with a biopharmaceutical's production (purification, formulation, vialing, and storage; see Figure 2.7B). Consequently, if the manufacturer of an innovative biopharmaceutical uses scenario #1 to make "m" lots of its innovative biopharmaceutical that are each uniquely labeled with a different lot identification number rather than scenario #2, then a biosimilar manufacturer analyzing more than one of those "m" uniquely labeled commercial RP lots would effectively be analyzing the *same* RP lot more than once. As a result, the mean value measured for any attribute (parameter or plot) that characterizes the RP will be falsely skewed (to some extent)