in the innovator's biopharmaceutical or reference product (RP; Federal Register, 2009) and the range of variability of these PTMs on a lot-to-lot basis. Once assessed, the biosimilar manufacturer will then need to find the best cell line in combination with appropriate bioreactor growth conditions that will produce a biosimilar that adequately matches the RP's entire physicochemical structure and its structural heterogeneity when both the biosimilar and RP are analytically characterized. This package of analytical physicochemical information will include common analytical release testing data [required for all biopharmaceuticals submitted for regulatory approval, e.g., size-exclusion chromatography (SEC), sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)], as well as additional characterization testing. In many cases, this extended characterization work will involve the use of advanced state-of-the-art analytical methods, potentially capable of delivering detailed fingerprint physicochemical structural information that was very likely not even available to the innovator when their drug was first approved. In addition, the redundant assessment of some key physicochemical parameters will also very likely be needed using orthogonal analytical methods to assure confidence in the resulting data.

Although the fine-detail structural information on an innovator's biopharmaceutical readily exists with the innovator and to a large extent with the regulators who reviewed the chemistry, manufacturing, and control (CMC) section of the biopharmaceutical's biological licensing application (BLA) and gave their approval to the innovator to allow its commercial marketing, this information (as previously noted) is not publicly available, nor are the regulators legally allowed to reveal it. The only route for a biosimilar manufacturer to obtain this information is to access it through its own analytical work that it conducts on RP material available commercially during the time period in which a biosimilar manufacturer is committed to developing its biosimilar. Hence, a biosimilar company must go out on the open market and purchase an appropriate amount of innovator drug material from a sufficient number of different innovator lots, potentially resulting in a significant cost to the biosimilar company (amounting to millions of dollars to cover biological, physicochemical, and limited clinical testing). These lots should preferably span the widest range of manufacturing time in terms of years and lot age as possible to adequately assess the historical and intrinsic manufacturing variability of the RP. Indeed, such variability will likely include the occasional manufacturing process changes made by the innovator (Crommelin et al., 2015; Schiestl et al., 2011; Schneider, 2013; Tebbey et al., 2015) and possibly unknown small deviations in the manufacturing process of the RP that can accumulate over time to give rise to what is called *drift* in some physicochemical attributes of the RP (Ramanan and Grampp, 2014; Ventola, 2013). In many of these measurements, head-to-head comparisons between representative lots of the biosimilar and RP should be conducted at the same time on the same instrument. Such head-to-head comparisons minimize the analytical method's day-to-day variability and even instrument to instrument variability (Ghirlando et al., 2013; Zhao et al., 2015) that could obscure and even bias the analytical data generated.

Once the physicochemical window of consistency for the RP is established (which in principle should be considered an "apparent" physicochemical window of consistency, owing to the inherent limitations a biosimilar manufacturer will face in securing the complete variable history of the RP; see Sections 2.5.1.3 through 2.5.1.5),