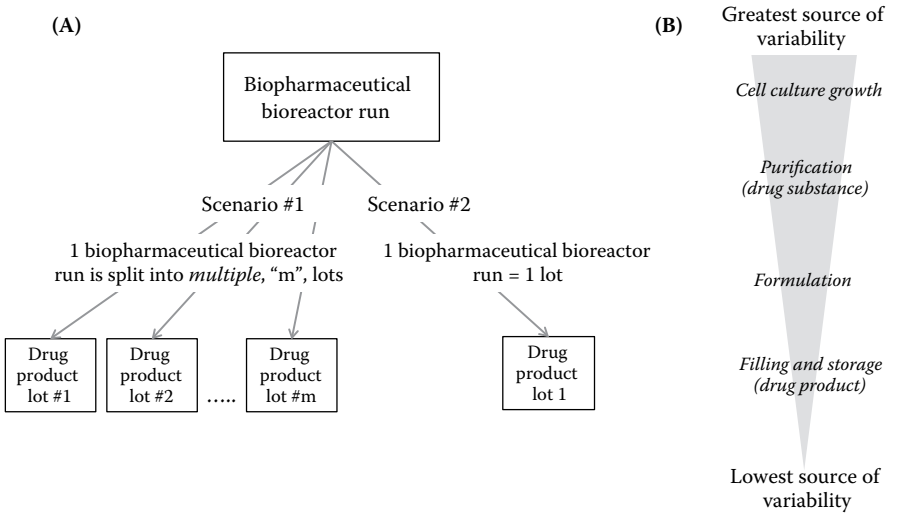

FIGURE 2.7 Understanding the potential relationships of uniquely identified biopharmaceutical drug product lots that are released by an innovator for commercial use to the bioreactor run from which they are derived. (A) Scenario #1: one large bioreactor run is used to make multiple commercial biopharmaceutical drug product lots that are each labeled by a uniquely different identification number versus scenario #2: one bioreactor run is used to only make one uniquely identified and labeled commercial biopharmaceutical drug product lot. (B) A rough rank ordering of the factors that contribute to the physicochemical variability in the production of a biopharmaceutical drug product lot, listed in order where the top factor typically introduces the most variability, while the bottom factor typically introduces the least variability.

by the inappropriate weighting (bias) created by those repeated measurements on effectively the same RP lot. In addition, the resulting measured lot-to-lot variability of any physicochemical attribute evaluated in such a situation will also be biased to a lower value.

2.5.1.5 RP Sourcing Limitations for Different Regulatory Regions

The final challenging complication in the biosimilarity process is associated with the issues surrounding the sourcing requirements (or limitations) of the RP material that can be used in a biosimilar filing in each country or geographical region that a specific regulatory agency oversees. In most cases, the RP lots that can be used by a biosimilar company must be from lots that were specifically approved in the regulatory region where the biosimilar manufacturer will be filing its biosimilar. Since innovator biopharmaceuticals are commonly made at more than one site, which only service certain specific regulatory regions, this can create problems for the biosimilar manufacturer who wants to file its biosimilar globally (Greer, 2012). In this case, the RP physicochemical data package used for one regulatory region may not be able to readily be applied to another regulatory region. However, some regulatory agencies will allow their inclusion if appropriate bridging data can be provided,