effects, especially in the case for biophysical methods, and remove method-specific interfering excipients. In general, such sample-handling and processing steps can create their own potential problems, especially when not applied in an identical manner to all of the samples being compared. As a result, any asymmetry in the way the RP and biosimilar are handled and processed can lead to erroneous conclusions concerning the presence or absence of biosimilarity and to erroneous data for setting target specification values and/or range limits for physicochemical parameters used in biosimilarity assessments. As a result, it will be important for the biosimilar manufacturer to validate any sample handling and processing used during any physicochemical measurement to assure that it does not alter the RP and/or biosimilar (Heavner et al., 2007; Panjwani et al., 2010).

2.5.1.3 Potential Impact of Investigating a Limited Number of RP Lots

A challenging characteristic of the process of assessing biosimilarity relative to the traditional exercise of (internal) comparability is due to the inability of the biosimilar manufacturer to have access to the complete historical knowledge base of information about the RP it is trying to copy (which encompasses lots made during research and development, e.g., toxicology and IND studies, and the complete commercial lot history of an innovator's biopharmaceutical). This is indicated in Figure 2.3 by the fact that the total number of all RP lots produced by an innovator, represented by *M*, is always going to be much greater relative to the total number of lots that can be secured by a biosimilar manufacturer for its characterization work on the RP, represented by *N*.

Over the time span in which an innovator develops and commercializes those *M* lots, a number of intentional changes in the production of the innovator material are very likely to have occurred (Crommelin et al., 2015; McCamish and Woollett, 2012; Schneider, 2013; Tebbey et al., 2015), along with some unintentional small level of drift in its manufacturing (Ramanan and Grampp, 2014; Ventola, 2013) process. If lot samples of the RP material obtained by a biosimilar manufacturer do not span the entire range of this variability, the physicochemical window of consistency assessed by the biosimilar manufacturer will likely be different and show a biased reduced variability in comparison to what the innovator has historically experienced, established, and employed in dealing with its regulatory filings. This is a likely outcome simply because biopharmaceutical lots typically have a commercial expiry (shelf life) of only about 2 years. Coupling this with the fact that a drug's patent protection can cover over a decade and possibly more of commercial lot production, a biosimilar company is only likely to be able to get access to a fairly limited fraction of the total number of commercial lots made (that have not expired). In addition, this limited fraction of RP lots will be dominated by lots corresponding to those made only in the latter years of production of an RP unless the biosimilar manufacturer had the foresight and willingness to start collecting samples of innovator RP lots a number of years before it actually started its biosimilar development program. Furthermore, those lots will also need to be analyzed before they expire, since RP lots analyzed after their expiration date may well raise questions as to the validity of the information they contribute to biosimilarity studies.