as the pre- and postchange biopharmaceuticals are comparable to each other (i.e., they meet the same set of limits or specifications). The former task is an important requirement that is conducted at various stages of development and commercialization of a biopharmaceutical to demonstrate to regulators that the biopharmaceutical manufacturer can successfully control its drug's manufacturing process to make a consistent drug product. The latter task is important in enabling a biopharmaceutical manufacturer to introduce a manufacturing change(s) during its development and still be allowed to proceed with filing a new investigational drug application (IND) to conduct clinical trials without the need to repeat earlier clinical work or to allow a manufacturer of a commercial biopharmaceutical product to introduce a change(s) into its drug's manufacturing process without having to provide additional clinical data.

In the situation where a *different* manufacturer (biosimilar manufacturer) is trying to make a copy of a biopharmaceutical, one could also consider this a process or manufacturing change in making the *same* biopharmaceutical. In this case, however, the *change* in the process is in the *company* that is making the biopharmaceutical. As a result, in this comparability exercise (which would be performed by the biosimilar manufacturer, to show regulators that both forms of the same biopharmaceutical are in fact comparable or highly similar) the innovator's biopharmaceutical would be the prechange biopharmaceutical and the biopharmaceutical copy of the innovator drug (biosimilar) would be the postchange biopharmaceutical. In principle this type of comparability could be conducted using the same science and regulatory concept as that employed in any normal comparability study. In fact this is the approach taken by the European Medicines Agency (EMA) in assessing biosimilarity (Berkowitz et al., 2012; McCamish and Woollett, 2013). As a result, the process of assessing biosimilarity can also be regarded as a comparability study. Nevertheless, a critically important difference exists when a different manufacturer (biosimilar manufacturer) attempts to make a copy of an innovator's biopharmaceutical. The important difference is that all of the information concerning the prechange biopharmaceutical (the innovator's biopharmaceutical) exists *external* to the biosimilar manufacturer making the postchange biopharmaceutical (biosimilar), which differs from the situation when an innovator conducts a comparability study, where all the information about the prechange and postchange forms of the same biopharmaceutical exist *internal* within the same drug company (the innovator). In such a situation one could consider the comparability conducted by an innovator as an *internal comparability* and comparability conducted by a biosimilar manufacturer as an *external comparability*. However, the ramifications of this difference are unique and important (Declerck, 2016), leading the FDA to see comparability or internal comparability as uniquely different from external comparability, and thus refer to the former as a comparability study, process or exercise and the latter as abiosimilarity study, process or exercise, see Figure 2.3.

In considering the concepts of comparability and biosimilarity, it is helpful to note a rare situation that arose in the early 1990s that in some ways links or bridges these two concepts. This rare situation came about when Rentschler in Germany contracted or partnered with another company, Biogen, in the US to develop and produce a potential innovative biopharmaceutical called interferon beta-1a (IFNβ)