reduced effectiveness" and "no higher side effects" upon switching and alternating. It will take a few years for details of what is considered appropriate to be established, but in the future, it is more likely that these products will be readily substituted, very much the small molecule generic products. Figure 4.14 shows a broader view of interchangeability.

However, taking into consideration the current statutory requirements embedded in the guidance limits what is required to establish interchangeability. Besides the two requirements stated earlier, the statute further states "in a clinical setting," which is construed as testing in patients. These three requirements can be enabled by clinical effectiveness studies (as opposed to clinical efficacy trials) that must be conducted to demonstrate that "switching and alternating" is acceptable.

The concept of *switchability* used for small molecules does not apply to biosimilars. From the FDA's perspectives, interchangeability includes the notion of switching and alternating between a reference licensed product (R) and biosimilar test product (T). The concept of switching is referred to like the switch from not only R to T or T to R (narrow sense of switchability) but also T to T and R to R (broader sense of switchability). As a result, in order to assess switching, biosimilarity for R to T, T to R, T to T, and R to R needs to be assessed based on some biosimilarity criteria under a

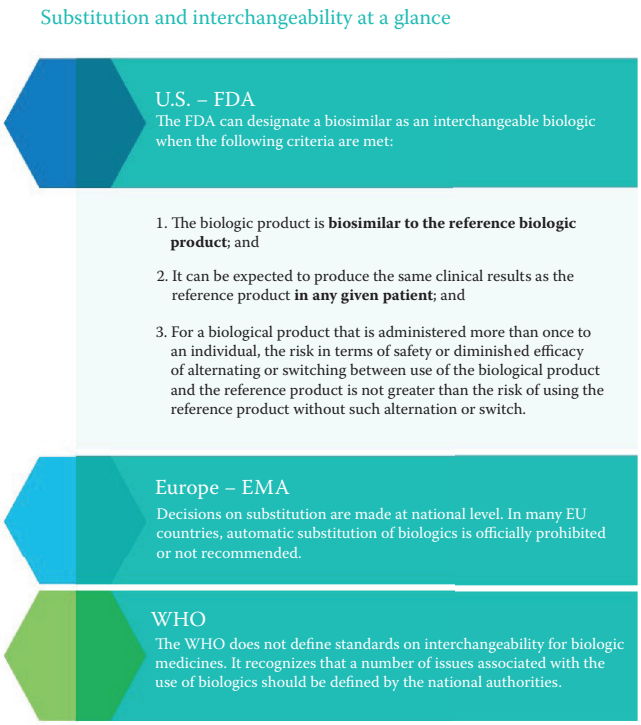

Figure 4.14 Interchangeability. (Courtesy of Amgen, Thousand Oaks, California, http://www.amgen.com/img/misc/biosimilars_06_large.jpg.)