variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.
- WHO: A biotherapeutic product, which is similar in terms of quality, safety, and efficacy to an already-licensed reference biotherapeutic product.

Both WHO and EMA require a product to be *similar*, while the FDA requires them to be at least *highly similar* to qualify as a biosimilar. Regarding the variability, the FDA states "no clinically meaningful difference … in terms of safety, purity and potency," and the EMA states "its variability … not to affect safety or effectiveness." The WHO emphasizes "quality, safety and efficacy," and makes the description more confounding than what is suggested by the FDA and the EMA. These subtle differences are important in understanding the mind-set of these agencies. Both the FDA and the EMA shun from using *quality*, which is a broad and perhaps an assumptive term. The FDA stays away from *effectiveness* or *efficacy*, while both the EMA and WHO emphasize it, although differently. It should be noted that the correct description is effectiveness that is demonstrated by comparison, whereas efficacy is a controlled clinical trial outcome against a placebo. Effectiveness can be shown by many methods including patient trials; efficacy is generally proven in patients only. This subtle difference is missed out in the WHO definition and in the guidelines of several other countries.

Recent draft guidance issued by the EMA (October 2014) brings the EMA closer to the thinking of the FDA to allow as many approvals without clinical trials in patients when justified. The rhetoric of the originators that extensive clinical trials are the only way to establish safety and efficacy (effectiveness) of biosimilar products is being set aside by the regulatory agencies. However, the onus of proving that a clinical trial is not needed, or only minimal trials are sufficient, lies on the sponsor of the biosimilar product, and it is, for this reason, the understanding of the science and the art involved in establishing evidence of biosimilarity is crucial for success.

4.2 The FDA mind-set

The BPCI Act of 2009 was passed as part of health reform (ACA) that President Obama signed into law on March 23, 2010. The BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product. A biological product that is demonstrated to be highly similar to an FDA-licensed biological product (the reference product) may rely on licensure, among other things, publicly available information regarding the FDA's previous determination that the reference product is safe, pure, and potent. This licensure pathway permits a biosimilar biological