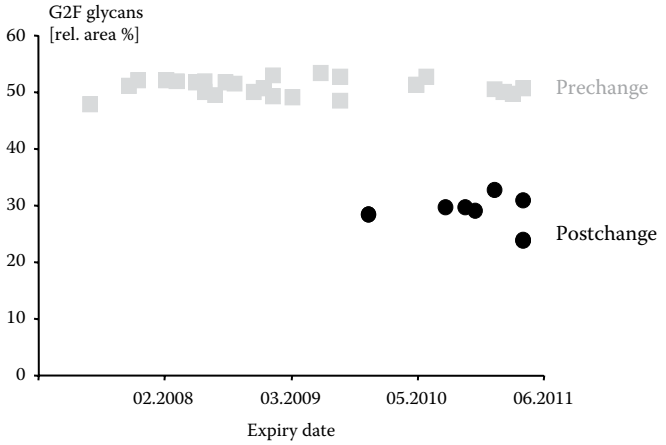

FIGURE 7.1 Comparisons of different pre- and postchange batches of Enbrel. (From Schiestl, M. et al., *Nature Biotechnology.*, 29, 310–312, 2011. With permission.)

when using the traditional clinical trial design for anti-TNF biologics in rheumatoid arthritis patients using ACR20 (American College of Rheumatology: 20% improvement) as the primary endpoint, such a difference in this particular glycosylation pattern would not impact efficacy. This absence of clinically meaningful differences, and hence the lack of sensitivity of clinical studies, is all the more apparent when this same established clinical metric is used to compare the clinical outcomes of various anti-TNF agents, each containing totally different active ingredient molecules. For example, Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), Cimzia (certolizumab pegol), and Simponi (golimumab) all produce similar clinical outcomes but have different active ingredients. These similar efficacy results with quite different molecules provide convincing evidence that the clinical trial is far less sensitive in picking up differences between biologics whether originator or biosimilar than analytical studies (Figure 7.2). One has to conclude that different molecules can produce the same clinical outcomes, but the same molecules cannot produce different clinical outcomes.

7.2.2 The Contribution of Clinical Trials—A Paradigm Shift

Historically, clinicians are trained to look at clinical data when making choices about which drug to use; therefore, they look predominantly for clinical data. However, for biosimilars the clinical trials are not the primary data on which regulatory approval is based. For biosimilars the clinical trials are not designed in the same way as those trials used for approval of novel drugs. The evaluation of clinical trials for biosimilars by both regulators and clinicians requires a paradigm shift, as stated by Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER) at the US Food and Drug Administration (Woodcock, 2012). This paradigm shift requires physicians to understand that the clinical trial for approval of a biosimilar drug is