



Figure 10.2 Dependency of effectiveness and safety of biosimilars.

### 10.3 No phase 3

Perhaps the most significant aspect of the FDA perspective on biosimilarity comes from a view that is diametrically opposed to what other regulatory agencies consider pivotal—the phase 3–type trials. Recently, agencies such as EMA have begun to take the same stance but with a lot of hesitation and without the FDA frankness in making decisions.

The biosimilar application for epoetin alfa was submitted by Hospira to the FDA on December 16, 2014. It was Hospira’s first submission for a biosimilar in the United States and submitted as an abbreviated BLA. This product has been available in Europe since 2008 under the name *Retacrit* for the treatment of anemia associated with chronic renal failure. On its quarterly earnings call, Pfizer (now the owner of Hospira) revealed that the FDA has rejected Hospira’s application. In securing approval in Europe, Hospira ran phase 3–type studies in thousands of patients and had a history of over 6 years of use in a large patient population, yet all of this was not enough to convince FDA; the lesson we learned is that phase 3 trials do not replace any residual uncertainty and a proof of clinical effectiveness does not overcome the tier-based biosimilarity assessment (<http://www.bigmoleculewatch.com/2015/10/27/fda-rejects-hospiras-epogen-biosimilar/>).

The reason why the FDA does not anticipate seeing any phase 3–type trials is based on several considerations:

- New drug approval requires demonstration of efficacy and adverse events for each indication, forming a basis for risk analysis; each indication requires a separate clinical trial.
- Biosimilar clinical testing will require NI testing against the reference, *not* the placebo, increasing the need for a larger population—the question, can one trial be sufficient to allow all other claims? arises.
- To allow all claims, the molecule must be highly similar to the reference molecule with no residual uncertainty, and that can