Table 9.1 Equivalence Interval Analysis of EP2006 by the FDA

Test (# Lots)	Reference (# Lots)	Confidence Level, % $(1–2\alpha)*100$	CI, %	Acceptance, %, $1.5*\alpha_R$	Result	*R/T* Ratio
EP2006 clinical (11)	U.S. Neupogen (12)	90	–1,75, +0.70	±2.26	Pass	1.09
EP2006 commercial (6)	U.S. Neupogen (12)	81.4	–3.87, –1.13	±2.08	Fail	2
EP2006 clinical (11)	EU Neupogen (11)	90	–2.32, +0.52	±3.23	Pass	1
EU Neupogen (49)	U.S. Neupogen (12)	90	+0.27, +2.09	±2.26	Pass	0.24
EP2006 clinical + commercial (20)	U.S. Neupogen (12)	90	–1,87, +0.15	±2.26	Pass	0.6
EP2005 clinical + commercial (20)	EU Neupogen (49)	90	–2.98, –0.85	±3.23	Pass	2.45
EU Neupogen (49)	U.S. Neupogen (12)	90	+0.27, +2.09	±2.26	Pass	0.24
EP2006 clinical (13)	U.S. Neupogen (12)	90	–1.78, +0.43	±2.26	Pass	0.92
EP2006 clinical (13)	EU Neupogen (49)	90	–3.13, –0.53	±3.26	Pass	3.7
EP2006 commercial (7)	U.S. Neupogen (12)	85.2	–2.33, +0.67	±2.28	Fail	1.7
EP2006 commercial (7)	EU Neupogen (49)	85.2	–3.71, -0.20	±3.23	Fail	7

Last column was added by the author.

Source: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM428780.pdf)

that the clinical lots meet the U.S. and EU Neupogen. When the U.S. and EU Neupogen meet together, the clinical and commercial lots meet, and therefore they can be combined (dark gray shaded rows).

A good example is the comparison of the total protein content of filgrastim between two products (Figure 9.5).

Since protein content is also a release attribute, a dilemma arises for the developers, where the release criteria are established independently of the comparison with the reference product. It would be suitable for a release specification to list the acceptance criteria as ±5%, yet the product, at the evaluation stage, must not have higher variability than the reference product. What if the reference product has an extremely low standard deviation? Multiplying it by 1.5 still provides a very narrow range for the biosimilar candidate to fit the similarity. An extreme example, not out of possibility, comes when say 10 out of 10 lots of the reference product have exactly the same protein content; with a SD of zero, every biosimilar candidate will fail. The reason why this observation