2.2.5.6 One-size-fits-all versus case-by-case

The FDA has clearly enunciated that all evaluation of biosimilar products will be made on a case-by-case basis. The root of this decision lies in the extreme diversity in the type of molecules involved; for example, a simpler molecule like filgrastim that has little immunogenicity potential and presents an excellent pharmacodynamic modeling will be assessed differently than adalimumab, a 148 kDa molecule with variations in its glycoforms, antibody-dependent cell-mediated cytotoxicity (ADCC), and lysine components; also, the in vivo nonclinical testing can be significantly different, such as for adalimumab, wherein a suitable animal toxicology model does not exist.

2.2.5.7 Totality of the evidence

The FDA coined the phrase *totality of the evidence* in 2007 when it licensed Avonex stating in *Nature Reviews: Drug Discovery*:

> On the basis of these data, the FDA concluded that the totality of the evidence indicated that the Bioferon product and Avonex were sufficiently comparable to rely on the data from major efficacy study using Bioferon's product to support licensure of Avonex.

In 2011, the FDA stated in an article in *New England Journal of Medicine Nature Reviews*:

> The FDA has traditionally relied on integrating various kinds of evidence in making regulatory decisions. Such a "totality-of-the-evidence approach. . . ."

In 2012, when the FDA issued a draft guidance that was later formalized in 2015, the FDA continues to emphasize that the approval of biosimilars will be made based on the totality of the evidence, the burden of proof lying with the sponsor.

2.2.5.8 No clinically meaningful difference

Fully recognizing that lot-to-lot differences in the originator product demonstrate that some differences are not clinically meaningful since the originator product with these differences has gone into the patient without any adverse events associated with these differences. When a biosimilar product is evaluated and it demonstrates differences, a discussion ensues whether this difference is clinically meaningful or not. This consideration is an extremely sensitive issue since the FDA is privy to what constitutes a minor variation, which the biosimilar product developer may not know. It is for this reason that the FDA wants the sponsors to analyze a sufficient number of originator lots bearing different expiry dates, to fully evaluate the nature and the extent of variability in the originator product. Some variations are well known to be less meaningful such as the presence of norleucine in filgrastim, or the ADCC