of biosimilarity as suggested by the FDA. The specific language used to describe each tier is pivotal in understanding the regulatory consequences.

4.5.1 Level 1: Not similar

At Level 1, the functional similarity is not in line with the reference product. This includes bioassays, in vitro binding tests, glycan patterns, and immunogenicity profile for products for which immunogenicity is a concern. The determination by the Agency whether a product is not similar can be challenged by the sponsor, but it will require extensive toxicology studies and other nonclinical evaluations, many of which may be difficult to plan in the absence of an understood MOA. For example, mAbs are difficult to evaluate at the nonclinical testing level because of lack of a suitable toxicology model in common species used for such studies. The developer needs to evaluate the cost of challenging this tier status vis-à-vis the cost of a 351(a) filing.

4.5.2 Level 2: Not highly similar

This tier stipulates "additional analytical or other data needed to determine if the product is not highly similar to the reference." This discussion with the Agency will likely take place in a Type 2 meeting where the sponsor presents an orthogonal evaluation of the biosimilar candidate comparing it with the reference product. Whereas it is not the expectation that all orthogonal tests will provide an equal level of similarity, the purpose of this classification is to encourage the sponsor to move to the highly similar tier, the minimum tier required to be classified as a biosimilar product.

The developer would be required to present a detailed plan of testing that is expected to provide confidence that the product can be classified as Level 3, and any differences that are observed are not clinically meaningful. This judgment is subject to interpretation and highly determined by the anticipated clinical responses. In those instances where the product is administered on a chronic basis, the residual uncertainty can be reduced by conducting protocols that require switching between the reference and the test products, particularly in animal models, to demonstrate that any functional dissimilarity is not clinically meaningful.

Generally, the product must meet most of the primary, secondary, and tertiary structural similarities and most of the functional similarity. The additional studies as recommended are intended to support the assertion that the observed variability is not exacerbating any toxic or immunogenic response and that repeated use will not result in a noticeable inferior clinical response.

In all instances, these additional tests will depend on the type of product, such as cytokine versus mAb, and will incur the substantial additional expense to prove similarity.