3.3 TIER ASSIGNMENT FOR CRITICAL QUALITY ATTRIBUTES

Tsong (2015) indicated that CQAs are necessarily tested for the functional, structural, and physicochemical characterization of the proposed biosimilar product as compared to a reference product (either a US-licensed product or an EU-approved reference product) for analytical similarity assessment. Analytical similarity assessment is considered to be the foundation of the stepwise approach for obtaining the totality of the evidence for demonstrating biosimilarity between the proposed biosimilar product and the reference product. Gutierrez-Lugo (2015) provided a list of CQAs and methods used to evaluate the analytical similarity of the proposed biosimilar product (EP2006) as compared to a US-licensed Neupogen and EU-approved Neupogen (see Table 3.1). These CQAs are assessed for analytical similarity by means of the so-called tier approach.

3.3.1 Criticality Risk Ranking

The tier approach first assesses the criticality risk ranking of the CQAs relevant to clinical outcome and classifies these CQAs to appropriate tiers depending on their impact (degree of criticality risk ranking) on clinical outcomes. The CQAs with most relevance to clinical outcomes will be assigned to Tier 1, while the CQAs with mild to moderate relevance to clinical outcomes will be classified as Tier 2. Tier 3 will contain those CQAs with the least relevance to clinical outcomes. In practice, it is believed that biological activity assays are the best representation available to test the clinically relevant mechanism of action (MOA) and therefore should be assigned to Tier 1. Other CQAs that are tested in comparative physicochemical and functional assessment (outside of those relevant to MOA) are of potential relevance to similarity, which are considered most appropriate for Tier 2 or Tier 3.

The FDA, however, has suggested a critical risk ranking of quality attributes with regard to their potential impact on activity, PK/PD, safety, and immunogenicity, with quality attributes being assigned to tiers commensurate with their risk. As a result, it is suggested that a statistical approach should be considered to serve as a decision tool for certain CQAs that are relevant to the demonstration of similarity. In other words, it is suggested that an appropriate statistical model should be used not only to determine the relevance or association between CQAs and clinical outcomes but also to assess the criticality risk ranking of the CQAs relevant to clinical outcome by establishing a predictive model. The established predictive model can then be used to determine the degree of criticality risk ranking for assignment of the identified CQAs to appropriate tiers.

3.3.2 Statistical Model

According to the *United States Pharmacopeia* (USP), *in vitro* and *in vivo* correlation (IVIVC) is referred to as the establishment of a relationship between a biological property, or a parameter derived from a biological property produced from a dosage form, and a physicochemical property of the same dosage form (USP/NF, 2000; Chow and Liu, 2008). Typically, AUC (area under a blood or plasma concentration-time curve) or peak concentration (C_{max}) is considered the parameter derived from the biological property, while the physicochemical property is the *in vitro* dissolution profile.