The criteria for approval of a biosimilar biologic differ between national regulatory authorities, and biosimilar mAb drugs that have been approved in India (Reditux/Rituxan) and South Korea (Remsima/Remicade) have not been automatically approved by the EMA or the FDA. However, the biosimilar candidate for Remicade (Remsima, Celltrion; Inflectra, Hospira), which was developed under EMA guidelines, received EMA approval in 2013 (Beck and Reichert, 2013; Hospira, 2013). Approval was heralded as a "landmark" event and demonstrates that the EMA has confidence in its ability to evaluate the comparability of biosimilar antibody products; the FDA has recently also scored a "first" in approving Zarxio (filgrastim-sndz), a biosimilar of Filgastrim (FDA, 2015a).

4.2 OVERVIEW OF CO- AND POSTTRANSLATIONAL MODIFICATIONS

Variations in protein structure from that predicted by open reading frame gene sequences are frequently referred to, collectively, as posttranslational modifications. However, heterogeneity may be introduced at an earlier stage [e.g., by misincorporation at the DNA, RNA, amino acid levels and cotranslationally (Harris et al., 2001; NCI, 2016; Zhong and Wright, 2013)]. Commonly encountered co-, post-translational (CTM/PTM), and chemical modifications (CMs) include glycosylation, phosphorylation, sulfation, glycation, deamidation, and deimination (Goetze et al., 2012; Harris et al., 2001; Jefferis, 2012; Khawli et al., 2010; NCI, 2016; Wang et al., 2007; Zhong and Wright, 2013). Additionally, the structural profile may vary with age, sex, health, and disease. The human genome contains ~21,000 protein encoding genes, but it is estimated that the human proteome consists of 1–2 million protein entities, due to the earlier mentioned parameters plus *in vivo* enzymatic and chemical modifications that are essential to systemic physiological function and/or within microenvironments (Harris et al., 2001; NCI, 2016; Zhong and Wright, 2013). Each human individual should, in theory, be immunologically tolerant to all molecules within their proteome, including those exhibiting PTMS and CMs. However, the exquisite sensitivity of current assay systems allows the detection of low-affinity antibody to many self-antigens in healthy individuals. Paradoxically, although healthy individuals exhibit immunological self-recognition antibodies of the same or similar, specificity may be amplified in disease states and be a diagnostic marker for individual disease entities (Burska et al., 2014).

The enumeration of PTMs and CMs generating P/GP heterogeneity has been achieved by "revolutionary" developments in qualitative and quantitative mass spectrometry, with definition of >300 structural CTM/PTMs (Chicooree et al., 2015; Lanucara and Eyers, 2013); analysis of 530,264 sequences in the Swiss-Prot database was shown to yield 87,308 experimentally identified PTMs and 234,938 putative PTMs (Chicooree et al., 2015; Farriol-Mathis et al., 2004; Khoury et al., 2011; Lanucara and Eyers, 2013). The potential for structural and functional complexity can be appreciated from the fact that the human genome encodes 518 protein kinases and 200 phosphatases (Manning et al., 2002; Sacco et al., 2012). The second most frequent CTM/PTM is glycosylation. Oligosaccharides may be attached to