be that it is representative of the endogenous molecule active *in vivo*. In practice, a consensus structure for the functional molecule is established as the goal for the development and characterization of a potential recombinant therapeutic. It is mandatory that recombinant P/GP therapeutics exhibit consensus PTMs of the endogenous molecule, with an absence of unnatural PTMs introduced in the production process. If present, the unnatural PTMs may be perceived as nonself by the immune system and result in the generation of ADA. Differences between the recombinant and the "wild-type" molecule are inevitable since recombinant proteins are produced in nonhuman tissues (CHO, NS0, Sp2/0 cells, etc.) exposed to culture medium, the products of intact and effete producer cells, and subjected to rigorous downstream purification, formulation, and storage conditions. Production in a prokaryotic system (e.g., *E. coli*) may result in a protein being recovered as an inclusion body that has to be solubilized and refolded *in vitro* to yield a product that may lack natural PTMs or bear unnatural ones.

In addition to the demonstration of clinical efficacy, an innovator company seeking approval for a potential P/GP therapeutic is required to characterize the drug substance/product structurally and functionally, employing multiple orthogonal technologies. The parameters established define the drug substance/product and, if approved, must be maintained throughout the life cycle of the drug; intentional changes in the production process may be approved by a regulatory authority if it is demonstrated not to compromise efficacy and patient benefit. Consequently, critical quality attributes (CQAs) that contribute to drug efficacy are defined and achieved, employing quality by design (QbD) parameters unique to the production platform, downstream protocols, and formulation employed. The CQA and QbD parameters are the undisclosed intellectual property of an innovator company. Consequently, in principle, it is deemed essentially impossible to produce an identical product employing a similar or alternative platform within another facility, i.e. it is not possible to develop generic biopharmaceuticals. The high cost and large size of the markets for biologics has encouraged "pharma," big and small, to develop biosimilar or follow-on biologic products, and regulatory authorities have developed competence in advising pharma and approving these products (EMA, 2008; FDA, 2014). It is often asserted that for the innovator product "the process defines the product"; for a biosimilar, it may be said that "the product defines the process." As the mechanism(s) of action (MoA) of P/GPs is being elucidated, protein and glycosylation engineering is being employed to develop next-generation molecules exhibiting selected and/or accentuated MoAs. This could be an oversimplistic approach because a mutant molecule is, by definition, an unnatural entity and the totality of its activities *in vivo* may not be the same as the endogenous molecule; it may exhibit enhanced immunogenicity, with consequent induction of ADA that could compromise efficacy and the patient.

It is accepted that "copies" of biologics cannot be structurally identical to an innovator product; however, regulatory authorities demand that they be demonstrated to be "comparable" to the innovator product (EMA, 2008; FDA, 2014). Structural comparability is established by applying multiple orthogonal analytical protocols to characterize the innovator product, sourced from a pharmacy in comparison with the proposed biosimilar. Inevitably, structural differences will be detected that must be demonstrated not to compromise functional efficacy, *ex vivo*, or patient benefit.