species specific and depends on the cell line and the culture conditions that are used for production. The presence and the structure of carbohydrate moieties can have a direct or indirect impact on the immunogenicity of therapeutic proteins, that is, the glycan structure itself can induce an immune response, or its presence can affect protein structure in such a way that the protein becomes immunogenic.

Glycosylation is an important factor in therapeutic protein immunogenicity. Glycans may impact the immunogenicity of therapeutic proteins in an indirect manner through their influence on folding, solubility, and structural stability of proteins. Besides making a protein more soluble, a carbohydrate moiety is sometimes able to cover an antigenic epitope.

7.2.2.3 Expression-related factors Fully functional mAbs also can be efficiently synthesized in transgenic plants. A major drawback of plant-derived glycoproteins is the presence of complex N-glycans with core xylose and core α1,3-fucose structures. These two glycoepitopes are foreign to humans due to differences in plant and mammalian glycosyltransferase repertoires.

The nonhuman glycan structures present on biopharmaceuticals can induce IgE-mediated reactions and/or anaphylaxis in allergic patients. Moreover, those glycoepitopes may enhance clearance and decrease therapeutic effect of biopharmaceuticals due to preexisting IgA, IgM, and IgG antibodies in certain patients. Neutralization of the therapeutic protein or cross-reactivity with the endogenous protein resulting from the presence of glycoepitopes is less likely, due to lack of reactivity toward the underlying protein backbone.

7.2.2.3.1 PEGylation Biopharmaceuticals can be chemically modified with the purpose of extending half-life or facilitating uptake by target receptors. An increasingly common type of engineering is the covalent attachment of polyethylene glycol (PEG) polymers to the peptide backbone. PEGylation adds additional molecular weight and lowers renal filtration resulting in the protection of proteins from proteolytic degradation. Similar to glycosylation, PEGylation may decrease immunogenicity by shielding the immunogenic epitopes while maintaining the native conformation of the protein. PEG polymers ranging in molecular weight from 12 to 40 kDa attached to different sites on the hydrophobic and immunogenic therapeutic proteins reduce the aggregation propensity and immunogenicity.

Some recombinant proteins are PEGylated in order to modify their PK. PEGylation of a protein is the process of attachment of PEG chains to the skeleton of the protein. The result is a decreased total half-life of the protein, protected proteolytic enzymes, and sometimes masked immunogenic sites. The new proteins so obtained differ by their conjugated structure, their molecular size, and their spatial conformation (linear,