Table 8.1 Impact of Various Formulation and Environmental Factors on the Degradation of Proteins

Factor	Impact
pH	Hydrolysis, deamidation
Buffer species	Deamidation
Other excipients	Maillard reaction
Light	Photodecomposition
Oxygen	Oxidation
Metal ions	Hydrolysis, oxidation
Temperature	Most routes

and it requires detailed studies, particularly those components that can enhance oxidation of proteins. Also significant for proteins is the physical degradation that can lead to significant safety issues.

Varieties of formulation factors that can induce instability are shown in Table 8.1. These factors are well studied and anticipated from the knowledge of the chemistry of all types of molecules. However, the impact on safety and efficacy is peculiar to biopharmaceuticals.

Compared to small-molecule drugs, biopharmaceuticals are typically more sensitive to slight changes in solution chemistry. They remain compositionally and conformationally stable only within a relatively narrow range of pH and osmolarity, and many require additionally supportive formulation components to stay in solution, particularly over time. Even lyophilized protein products are subject to significant degradation,

Table 8.2 Typical Stability Problems Observed in Protein Pharmaceuticals

Problems	Potential Causes	Possible Solutions
Noncovalent aggregation	Solubility, structural changes, heat, shear, surface, denaturants, impurities	pH, ionic additives, amino acids, surfactants, protein concentration, raw material purity
Covalent aggregation	Disulfide scrambling, other unknown mechanisms	pH, inhibit noncovalent aggregation
Deamidation	pH <5.0 or pH >6.0	pH optimization
Cyclic imide	pH around 5	pH optimization
Cleavages	Protease impurity, other unknown mechanisms	pH, product purity, inhibitors
Oxidation	Active oxygen species, free radicals, metals, light, impurity	Excipient purity, free-radical scavenger, active oxygen scavengers, methionine
Surface denaturation, adsorption	Low-protein concentration, specific affinity, protein hydrophobicity	Surfactants, protein concentration, pH