

WHITE PAPER

Ten major factors in successful protein formulation development

Each protein has its own “personality” whose contribution to physicochemical attributes and final drug product formulation is difficult to guess and/or fix without conducting systematic research. When a new protein is in the development phase, one would ask what should be the most effective and efficient process to identify a formulation given the resource, budget, and timeline. Listed below is key information required for developing good protein formulations.

1. Relevant stresses

Proteins are molecules of delicate three-dimensional structures that are made of unique primary, secondary, tertiary, and even quaternary structures. Because of this, different proteins may be susceptible to different stresses during normal pharmaceutical operations such as process, manufacturing, storage, transportation, and delivery. Therefore, it is important to understand what the relevant stresses for each individual protein are. Heat, cold, agitation, shear, surface, freezing, dehydration, and light are examples of relevant physical stresses. Metal ions, destabilizing impurities, pH, active oxygen species and free radicals are examples of some chemical stresses. The stresses introduced for formulation development studies have to be relevant to what the product will experience in real life.

2. Major degradation products

Proteins exposed to stresses generate various forms of degradation products. Physical degradation products include aggregation, precipitation, denaturation (loss of active conformation), and fragmentation. Chemical degradations include oxidation, deamidation, disulfide scrambling, and Maillard reaction. Other product-specific degradation products may also be produced.

3. Stability indicating assays

Good biophysical and biochemical markers to determine the loss of product integrity under normal pharmaceutical operation are essential for screening stable formulations. These stability-indicating assays include HPLC methods, electrophoresis, particle analyses, structural analyses, and bioassays.

4. Basic formulation parameters for stability

Among many different formulation variables, it is crucial to first identify the best combination(s) of pH, ionic strength, and surfactant(s). The “formulation sweet spot” has to be identified against all relevant stresses including actual storage stability studies.

5. Key inactive ingredient(s)

The best formulation should contain the least number of necessary ingredients that are selected based on their effectiveness in mitigating key issues as well as for achieving desired attributes. These include solubilizers, stabilizers, buffers, tonicity modifiers, bulking agents, viscosity enhancers/reducers, surfactants, chelating agents, adjuvants, etc.

6. Liquid or lyophilized

Liquid formulations are generally the preferred presentation although lyophilized formulations are more stable. The decision has to be strategic and based on the intrinsic stability of the protein, as not all proteins are stable enough for liquid formulation. Development of lyophilized formulation requires additional effort for the extra process. Different excipients are generally used for liquid and lyophilized formulation candidates.

7. Protein concentration

Final commercial dose is not available until the completion of clinical trials, so it is important to understand the feasible concentration window for the protein of interest. In general, the concentration is not as critical for intravenous

delivery products as subcutaneous or intramuscular delivery. It is generally preferred to achieve higher concentrations for the benefit of smaller packaging, reduced injection volume, and delivery time. However, it is more challenging to develop drug products at higher concentrations due to faster rates of aggregation and/or greater viscosity.

8. Delivery options

Different formulations may be developed for different delivery options. Local delivery may require additional functional additives in the formulation. Also, different container/closure systems may be preferred for different delivery options. Additional studies may be required to support the different delivery options, e.g., compatibility study with diluents and infusion sets for intravenous delivery. Nonparenteral delivery may require a specific device that may necessitate delivery-specific formulations.

9. Container/closure systems

Compatibility of proteins with the actual container/closure system will have to be confirmed by stability studies. These include direct containers like vials, prefilled syringes, cartridges, etc., and indirect delivery systems like diluent bags and infusion catheters, etc.

10. Intellectual properties

There are outstanding patent claims for the use of certain formulations. Therefore, it is prudent to have legal representatives to look into the freedom to operate or licensing opportunities for some formulation options. Some product specific formulation(s) may be eligible candidates for patent filing.

