

Formulation development for biologics — liquid and lyophilized formulations

The formulation development process characterizes the physiochemical characteristics which are unique to each molecule. For biologics, solutions generally can be prepared to the desired concentration with ease but the desired stability of the molecule in solution proves to be the greater challenge. As for any drug that is selected for development, formulation development will inform physico-chemical characteristics as well as options for administration, manufacturing process, and product costs. The SP Formulations (SPF) team has experience in developing a wide range of parenteral formulations (intravenous, intramuscular, subcutaneous) for peptides, proteins, and oligonucleotides.



Conserving the native three-dimensional structure of the molecule is the key criterion for a successful formulation, as this will maintain its biological activity. To optimize vehicle composition, SPF will assess formulating the molecule across a range of conditions, including variations in pH, identity and concentration of buffers, as well as identity and concentration of other excipients, such as bulking agents. The concentration of the molecule itself will also be considered. A series of small, matrix-like pre-formulation experiments will be executed and evaluated to determine suitable variables for more thorough formulation development experiments. Pre-formulation experiments can also be leveraged to select a lead composition from a class. Analytical methods to assess the formulation development process may be provided by the client or developed by SPF and should assess maintenance of the three-dimensional conformation as well as properties of the formulation itself. These include, but are not limited to, HPLC-based methods for concentration and purity (UV), aggregation state (SEC), DSC, particulate matter, osmolality, viscosity.

The general scheme includes an initial screen of buffers and excipients over 2-3 days, to investigate loss in concentration or purity. Better-performing solutions are then identified for more rigorous testing. If it is established that the molecule will not have adequate stability in solution, a lyophilized drug product will be developed. The development of a lyophilized drug product, including cycle development, takes into consideration the unique thermodynamic

properties of the API to deliver a successful formulation. This includes a robust and scalable fill solution, an efficient cycle that reliably provides the lyophilized product vials, a readily transferable process, as well as improved product stability and reconstitution characteristics.

In the development of formulated drug product, it is essential to leverage stability-indicating methods to ensure that degradation does not occur. If *a priori* your analytical method is not stability-indicating, forced degradation studies on the API can be done to help develop a suitable stability-indicating analytical method as well as identify potential degradation concerns. It will also be appropriate to conduct freeze-thaw cycles to provide options for bulk material handling. Aggregation, oxidation, and deamidation are main challenges to biologic molecule stability. Forced degradation techniques to mimic those conditions, as well as accelerated temperature, temperature cycling (freeze-thaw cycles), photostability, and both acid and base hydrolysis are used to induce and assess degradation. Prevention of known degradation pathways is a primary concern to the formulation development process. These forced degradation studies will ensure that the analytical methods, or modified versions thereof, are appropriate for short- and long-term stability studies.

The container-closure system will be considered during drug product development as the selected system can have an impact on the stability of the formulated product. Container types and temperature exposures during preparation of bulk formulation as well as unit product needs to be considered. Biologics are often produced “at capacity” due to costs of production campaigns. However, bulk material often needs to be stored and used in portions when drug product is required. Typically, stainless steel or disposable plastic containers are used. For drug products, glass vials are necessary for lyophilized products, but clear and amber can be tested, along with a variety of stopper compositions. For other products, different plastic compositions can be evaluated in addition to glass.

Formulation development is not a discrete, single activity in the long pathway from discovery to market. SPF takes a comprehensive view of the entire development process, from post-nomination pre-formulation experiments, through the formulation development process, to the final presentation of the formulated drug product. SPF will develop formulations to enable ADMET and preclinical testing (PK, PD) that will provide meaningful support of clinical trials; i.e. establishing appropriate dose levels. Optimized formulation compositions offer the required drug product stability for both long-term storage and time during which it is administered as well as assurance of the molecule’s activity.

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