Table 5-2 Main Steps Involved in the Formulation of a New Sterile Drug Product

1. Obtain physical properties of active drug substance
   a. Structure, molecular weight
   b. "Practical" solubility in water at room temperature
   c. Effect of pH on solubility
   d. Solubility in certain other solvents
   e. Unusual solubility properties
   f. Isoelectric point for a protein or peptide
   g. Hygroscopicity
   h. Potential for water or other solvent loss
   i. Aggregation potential for protein or peptide
2. Obtain chemical properties of active drug substance
   a. Must have a "validatable" analytical method for potency and purity
   b. Time for 10% degradation at room temperature in aqueous solution in the pH range of anticipated use
   c. Time for 10% degradation at 5°C
   d. pH stability profile
   e. Sensitivity to oxygen
   f. Sensitivity to light
   g. Major routes of degradation and degradation products
3. Initial formulation approaches
   a. Know timeline(s) for drug product
   b. Know how drug product will be used in the clinic
      i. Single dose vs. multiple dose
      ii. If multiple dose, will preservative agent be part of drug solution/powder or part of diluent?
      iii. Shelf-life goals
      iv. Combination with other products, diluents
   c. From knowledge of solubility and stability properties and information from anticipated clinical use formulate drug with components and solution properties that are known to be successful at dealing with these issues. Then perform accelerated stability studies
      i. High-temperature storage
      ii. Temperature cycling
      iii. Light and/or oxygen exposure
      iv. For powders, expose to high humidities
   d. May need to perform several short-term stability studies, as excipient types and combinations are eliminated
   e. Understand need for any special container and closure requirements
   f. Design and implement an initial manufacturing method of the product
   g. Finalize formulation
      i. Need for tonicity adjusting agent
      ii. Need for antimicrobial preservative
   h. Approach to obtain sterile product
      i. Terminal sterilization
      ii. Sterile filtration and aseptic processing

Table 5-3 Basic Guidelines to Consider in the Development of Parenteral Solutions of Proteins and Peptides (in Addition to Considerations Presented in Tables 5-1 and 5-2)

1. Learn and understand the basic physical and chemical properties of the biopharmaceutical active ingredient
2. Know the intended route(s) of administration and formulation requirements unique to each route (e.g., pH, osmolality, freedom from particles, viscosity, and volume)
3. Rationale and selection of formulation components
4. Effects of manufacturing process on stability of the active ingredient
5. Selection of final container and closure system
6. Effects of storage and distribution on product stability